Complete Summary

GUIDELINE TITLE

Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.

BIBLIOGRAPHIC SOURCE(S)

Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H, Centers for Disease Control and Prevention (CDC), National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009 Apr 10;58(RR-4):1-207; quiz CE1-4. PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK. Treating opportunistic infections among HIV-exposed and infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004 Dec 17;53(RR-15):1-118. [693 references]

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse (NGC): This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- April 14, 2009 – Rocephin (ceftriaxone sodium): The U.S. Food and Drug Administration (FDA) notified healthcare professionals of an update to a previous alert that addresses the interaction of ceftriaxone with calcium-containing products, based on previously reported fatal cases in neonates. Based on the results from recent in vitro studies, FDA now recommends that ceftriaxone and calcium-containing products may be used concomitantly in patients >28 days of age, using the precautionary recommendations noted because the risk of precipitation is low in this population. FDA had previously recommended, but no longer recommends, that in all age groups ceftriaxone

and calcium-containing products should not be administered within 48 hours of one another.

- September 11, 2008 – Rituxan (Rituximab): Genentech informed healthcare professionals of revisions to prescribing information for Rituxan regarding a case of progressive multifocal leukoencephalopathy (PML) leading to death in a patient with rheumatoid arthritis who received Rituxan in a long-term safety extension clinical study.
- July 24, 2008 – Ziagen (abacavir sulfate): The U.S. Food and Drug Administration (FDA) has notified the maker of abacavir and abacavir-containing medications of the need to add information to the current BOXED WARNING about the recommendation to test all patients for the HLA-B*5701 allele before starting or restarting therapy with abacavir or abacavir-containing medications.
- July 31, 2008, Erythropoiesis Stimulating Agents (ESAs): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- July 08, 2008, Fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin): A BOXED WARNING and Medication Guide are to be added to the prescribing information to strengthen existing warnings about the increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones for systemic use.
- January 24, 2008, Leukine (sargramostim): Voluntary market suspension of the current liquid formulation of sargramostim, a granulocyte-macrophage colony-stimulating factor (GM-CSF), because of an upward trend in spontaneous reports of adverse reactions, including syncope (fainting). The lyophilized form of the drug is not affected. See the U.S. Food and Drug Administration (FDA) web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Opportunistic infection (OI) associated with human immunodeficiency virus (HIV) infection, including:

- *Pneumocystis jirovecii* (formerly *carinii*) pneumonia (PCP)
- *Toxoplasma gondii* encephalitis
- Cryptosporidiosis
- Microsporidiosis
- *Mycobacterium tuberculosis* infection (TB) and disease
- Disseminated *Mycobacterium avium* complex (MAC) disease
- Bacterial respiratory disease
- Bacterial enteric disease
- Bartonellosis
- Syphilis
- Mucocutaneous candidiasis
- Cryptococcosis
- Histoplasmosis
- Coccidioidomycosis
- Aspergillosis
- Cytomegalovirus (CMV) disease
- Herpes simplex virus (HSV) disease
- Human herpes virus type 6 (HHV-6) and type 7 (HHV-7) disease
- Varicella zoster virus (VZV) disease
- Human herpesvirus type 8 (HHV-8) disease
- Progressive multifocal leukoencephalopathy caused by JC virus infection
- Human papillomavirus (HPV) disease
- Hepatitis C virus (HCV) infection
- Hepatitis B virus (HBV) infection
- Geographic OIs of special consideration, including malaria, *Penicilliosis marneffei*, leishmaniasis, isosporiasis, and Chagas disease

GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation
Management
Prevention
Risk Assessment
Screening
Treatment

CLINICAL SPECIALTY

Allergy and Immunology
Dermatology
Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Oncology
Ophthalmology
Otolaryngology

Pediatrics
Preventive Medicine
Surgery

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Managed Care Organizations
Nurses
Patients
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

To update and combine earlier versions of guidelines for the prevention and treatment of opportunistic infections in human immunodeficiency virus (HIV)-infected adults and adolescents, last published in 2002 and 2004

TARGET POPULATION

Human immunodeficiency virus (HIV)-infected adults (aged $\geq$18 years) and adolescents (aged 13 through 17 years), including pregnant women, with or at risk for opportunistic infections

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation/Risk Assessment/Screening

1. Laboratory tests (blood tests, bacterial cultures, microscopy, organism-specific staining)
2. Medical and travel history, including injection drug use
3. Contact and exposure history
4. Imaging studies (e.g., computed tomography, magnetic resonance imaging)
5. Screening for opportunistic infections (OIs) or sequelae of OIs

Prevention/Counseling

1. Exposure avoidance
2. Modification of risk behaviors

Treatment/Management

1. Disease-specific pharmacologic therapy (refer to the "Major Recommendations" field for specific medications and therapeutic regimens)
2. Nonpharmacologic interventions as appropriate (refer to the "Major Recommendations" field for specific indications), including:

- Directly observed therapy (DOT) for patients with tuberculosis
- Penicillin desensitization
- Cryotherapy with liquid nitrogen
- Trichloroacetic or bichloroacetic acid cauterization
- Surgical excision of lesions (including laser surgery)
- Loop electrosurgical excision procedure (LEEP)
- Cone biopsy
- Cerebral spinal fluid (CSF) examination
- Lumbar puncture or CSF shunting
- Vaccination with 23-valent polysaccharide pneumococcal vaccine, influenza vaccine, and hepatitis A vaccine

3. Treatment of symptoms
4. Management of adverse events
5. Supportive care, including hydration, nutritional support, counseling
6. Monitoring for recurrence, adverse reactions, and drug toxicities
7. Special considerations for pregnant women (e.g., Cesarean delivery)
8. Referral to specialists

MAJOR OUTCOMES CONSIDERED

- Change in CD4+ cell count
- Mortality
- Change in signs and symptoms
- Recurrence rate of infection
- Duration of infection
- Fetal risk, including transmission of infection to fetus, morbidity, and mortality
- Incidence of toxicities and drug interactions
- Rate of development of drug resistance
- Sensitivity and specificity of diagnostic methods
- Clearance rate of infectious organism

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence Supporting the Recommendation

I: Evidence from at least one properly designed randomized, controlled trial.

II: Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.

III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

These guidelines were prepared by the Opportunistic Infections Working Group under the auspices of the Office of AIDS Research Advisory Council (OARAC) of the National Institutes of Health (NIH). Group leaders and team members with expertise in specific opportunistic infections (OIs) were selected from the membership of the Working Group; each group reviewed the literature since the last publication of the prevention and treatment guidelines, conferred for several months, and produced draft revised guidelines.

Recommendations were reviewed and discussed by the Working Group at a meeting in Bethesda, Maryland, on June 25–26, 2007. A draft version of these recommendations was posted at AIDSInfo (http://aidsinfo.nih.gov/contentfiles/Adult_OI.pdf) on June 18, 2008. Since the June 18, 2008 posting, the draft recommendations were reviewed and updated by Working Group members and subject matter experts. Suggested updates were reviewed by the co-editors, who amended the report, as warranted.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of the Recommendation

A. Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
B. Moderate evidence for efficacy – or strong evidence for efficacy but only limited clinical benefit – supports recommendation for use. Should generally be offered.
C. Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the treatment or alternative approaches. Optional.
D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

These guidelines were reviewed by respective members of each panel to ensure the recommendations were complete and appropriate.

The final version of the report was further reviewed by the co-editors, the Office of AIDS Research, the National Institutes of Health (NIH); experts at Centers for Disease Control and Prevention (CDC); and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA) before final approval and publication.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The quality of evidence supporting the recommendations (I-III) and the strength of the recommendation (A-E) are defined at the end of the "Major Recommendations" field.

Note from the Centers for Disease Control and Prevention (CDC): The original guideline document includes eleven tables pertinent to the prevention and treatment of opportunistic infections (OIs), a figure that describes immunization recommendations (Figure 2), and an appendix that summarizes recommendations pertinent to prevention of exposure to opportunistic pathogens. Refer to the original guideline document for a summary of recommendations on prophylaxis to prevent first episode of opportunistic disease (Table 1); drug therapy for treatment and chronic maintenance therapy of acquired immune deficiency

syndrome (AIDS)-associated OIs in adults and adolescents (Table 2); recommended doses of first-line antituberculosis drugs for adults (Table 3); criteria for discontinuing and restarting OI prophylaxis for adults and adolescents with human immunodeficiency virus (HIV) infection (Table 4); common toxicities of agents for treatment and prevention of OIs (Table 5); substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of OIs (Table 6); antiretroviral anti-infective drug combinations that should be avoided (Table 7); dosage adjustment in renal insufficiency (Table 8); summary of pre-clinical and human data on and indications for OI drugs during pregnancy (Table 9); comparative characteristics of tuberculin skin test (TST) with interferon (IFN)-gamma release assays (IGRAs) (Table 10); and cytology and histology terms for Papanicolaou smears and cervical, vaginal, and anal tissue samples (Table 11).

Refer to the original guideline document for information on the epidemiology, clinical manifestations, and diagnosis for each OI discussed.

Major Changes in Guidelines Since Last Publication

Major changes include 1) additional emphasis on the importance of antiretroviral therapy (ART) for prevention and treatment of OIs, especially those for which specific chemoprophylaxis and treatment do not exist; 2) information on diagnosis and management of immune reconstitution inflammatory syndromes (IRIS); 3) information on IGRAs for the detection of latent *Mycobacterium (M.) tuberculosis* infection; 4) updated information on drug interactions affecting use of rifamycin drugs for prevention and treatment of tuberculosis (TB); 5) addition of a section on hepatitis B virus (HBV) infection; and 6) addition of a section on malaria to the OIs of geographic interest.

Effect of Antiretroviral Therapy (ART) on the Management of OIs

Initiation of ART in the Setting of an Acute OI (Treatment-Naive Patients)

No consensus has been reached concerning the optimal time to start ART in the presence of a recently diagnosed OI. One study suggests that unless other individual compelling contraindications are present, early initiation of ART near the time of initiating OI treatment should be considered for most patients with an acute OI, excluding TB. Other elements that should be considered when making this decision are degree of immunosuppression, availability of effective therapy for the OI, risk for drug interactions, overlapping drug toxicities, risk for the consequences of the development of IRIS, and willingness of the patients to adhere to their drug regimens. In cases of cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy (PML), Kaposi's sarcoma (KS), *Pneumocystis jirovecii* pneumonia (PCP), and invasive bacterial infections, the early benefits of ART outweigh increased risk related to these other factors and ART should be started as soon as possible. In the setting of TB disease, awaiting a response to OI therapy might be warranted before initiating ART.

Management of Acute OIs in Patients Receiving ART

When an OI occurs within 12 weeks of starting ART, treatment for the OI should be started and ART should be continued. When an OI occurs despite complete virologic suppression (i.e., late OI), therapy for the OI should be initiated and ART

should be continued. If the CD4+ response to ART has been suboptimal, modification of the ART regimen may be considered, although no evidence exists to indicate that changing the ART regimen in this setting will improve the CD4+ response. When an OI occurs in the setting of virologic failure, OI therapy should be started, antiretroviral resistance testing should be performed, and the ART regimen should be modified, if possible, to achieve better virologic control.

Special Considerations During Pregnancy

For pregnant women who have had an OI diagnosed and are not on ART, immediate initiation of ART with OI therapy should be encouraged to minimize the risk for perinatal transmission of HIV. Decisions about immediate versus delayed initiation of ART in pregnancy should include consideration of gestational age, maternal HIV ribonucleic acid (RNA) levels and clinical condition, and potential toxicities and interactions between ART and OI drugs.

After first-trimester exposure to agents of uncertain teratogenic potential, a detailed ultrasound examination at 18 to 20 weeks should be conducted to detect possible major anomalies. For women who receive drugs that have not been extensively evaluated during pregnancy, an ultrasound should be conducted every 4 to 6 weeks to assess fetal growth and fluid volume, with antepartum testing if growth lag or decreased fluid are noted. Women in the third trimester of pregnancy should be instructed in daily fetal movement counting to detect decreased activity that might indicate fetal compromise.

***Pneumocystis* Pneumonia (PCP)**

Preventing Exposure

Certain authorities might recommend that persons who are at risk for PCP not share a hospital room with a patient who has PCP, a recommendation based on animal studies and anecdotal human experience. Data are insufficient to support this recommendation as standard practice (**CIII**).

Preventing Disease

Initiating Primary Prophylaxis

HIV-infected adults and adolescents, including pregnant women and those on ART, should receive chemoprophylaxis against PCP if they have a CD4+ count of <200 cells/microliter (**AI**) or a history of oropharyngeal candidiasis (**AII**). Persons who have a CD4+ cell percentage of <14% or a history of an AIDS-defining illness, but do not otherwise qualify, should be considered for prophylaxis (**BII**). When monitoring CD4+ counts frequently (e.g., every 1 to 3 months) is not possible, initiating chemoprophylaxis at a CD4+ count of >200, but <250 cells/microliter, also should be considered (**BII**).

Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent (**AI**). One double-strength tablet daily is the preferred regimen (**AI**). However, one single-strength tablet daily also is effective and might be better tolerated than one double-strength tablet daily (**AI**). One double-strength tablet

three times weekly also is effective (**BI**). For patients who have an adverse reaction that is not life threatening, chemoprophylaxis with TMP-SMX should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting TMP-SMX should be strongly considered after the adverse event has resolved (**AII**). Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens (**BI**) or reintroduction of TMP-SMX at a reduced dose or frequency (**CIII**); as many as 70% of patients can tolerate such reinstitution of therapy.

If TMP-SMX cannot be tolerated, alternative prophylactic regimens include dapsone (**BI**), dapsone plus pyrimethamine plus leucovorin (**BI**), aerosolized pentamidine administered by the Respirgard II nebulizer (manufactured by Marquest, Englewood, Colorado) (**BI**), and atovaquone (**BI**). Atovaquone is as effective as aerosolized pentamidine or dapsone (**BI**) but is substantially more expensive than the other regimens. For patients seropositive for *Toxoplasma gondii (T. gondii)* who cannot tolerate TMP-SMX, recommended alternatives to TMP-SMX for prophylaxis against both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin (**BI**) or atovaquone with or without pyrimethamine plus leucovorin (**CIII**).

Oral pyrimethamine plus sulfadoxine also has activity in preventing PCP (**CIII**). This combination should not be used in patients with hypersensitivity to sulfonamides. Largely because TMP-SMX has superior safety, widespread availability, and is low cost, oral pyrimethamine plus sulfadoxine should be used rarely in the United States (U.S.) (**CIII**).

The following regimens cannot be recommended as alternatives because data regarding their efficacy for PCP prophylaxis are insufficient:

- Aerosolized pentamidine administered by other nebulization devices
- Intermittently administered parenteral pentamidine
- Oral clindamycin plus primaquine

However, clinicians might consider using these agents in unusual situations in which the recommended agents cannot be administered (**CIII**).

Discontinuing Primary Prophylaxis

Primary pneumocystis prophylaxis should be discontinued for adult and adolescent patients who have responded to ART with an increase in CD4+ counts to >200 cells/microliter for >3 months (**AI**).

Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/microliter (**AIII**).

Treatment of Disease

TMP-SMX is the treatment of choice (**AI**). The dose must be adjusted for abnormal renal function. Adding leucovorin to prevent myelosuppression during

acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate (**DII**). Oral outpatient therapy of TMP-SMX is highly effective among patients with mild-to-moderate disease (**AI**).

Mutations associated with resistance to sulfa drugs have been documented, but their effect on clinical outcome is uncertain. Patients who have PCP despite TMP-SMX prophylaxis are usually effectively treated with standard doses of TMP-SMX (**BIII**).

Patients with documented or suspected PCP and moderate-to-severe disease, as defined by room air pO_2 <70 mm/Hg or arterial-alveolar O_2 gradient >35 mm/Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific PCP therapy (**AI**). If steroids are started at a later time, their benefits are unclear, although the majority of clinicians would use them in such circumstances for patients with severe disease (**BIII**). Methylprednisolone at 75% of the respective prednisone dose can be used if parenteral administration is necessary.

Alternative therapeutic regimens for mild-to-moderate disease include 1) dapsone and TMP (**BI**) (this regimen may have similar efficacy and fewer side effects than TMP-SMX but is less convenient because of the number of pills); 2) primaquine plus clindamycin (**BI**) (the clindamycin component can be administered intravenously for more severe cases; however, primaquine is only available orally); 3) atovaquone suspension (**BI**) (this is less effective than TMP-SMX for mild-to-moderate disease but has fewer side effects). Patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency whenever possible before administration of primaquine. Alternative therapeutic regimens for patients with moderate-to-severe disease include clindamycin-primaquine or intravenous (IV) pentamidine (**AI**) (usually the drug of second choice for severe disease). Aerosolized pentamidine should not be used for the treatment of PCP because of limited efficacy and more frequent relapse (**DI**).

The recommended duration of therapy for PCP is 21 days (**AII**). Because long-term survival is possible for patients in whom ART is effective, certain patients with AIDS and severe PCP should be offered intensive care unit (ICU) admission or mechanical ventilation when appropriate (e.g., when they have reasonable functional status) (**AII**).

Because of the potential for additive or synergistic toxicities associated with anti-PCP and ARTs, certain health-care providers delay initiation of ART until after the completion of anti-PCP therapy, or until at least 2 weeks after initiating anti-PCP therapy, despite some suggestion of potential benefit for early ART in the treatment of PCP (**CIII**).

Monitoring and Adverse Events, Including IRIS

Careful monitoring during therapy is important to evaluate response to treatment and to detect toxicity as soon as possible. Follow-up after therapy includes assessment for early relapse, especially when therapy has been with an agent other than TMP-SMX or was shortened for toxicity. PCP prophylaxis should be initiated immediately upon completion of therapy and maintained until the $CD4^+$ count is >200 cells/microliter.

Adverse reaction rates among patients with AIDS are high for TMP-SMX (20% to 85%). Common adverse effects are rash (30% to 55%) (including Stevens-Johnson syndrome), fever (30% to 40%), leukopenia (30% to 40%), thrombocytopenia (15%), azotemia (1% to 5%), hepatitis (20%), and hyperkalemia. Supportive care for common adverse effects should be attempted before discontinuing TMP-SMX (**AIII**). Rashes can often be "treated through" with antihistamines, nausea can be controlled with antiemetics, and fever can be managed with antipyretics.

The most common adverse effects of alternative therapies include methemoglobinemia and hemolysis with dapsone or primaquine (especially in those with G6PD deficiency); rash and fever with dapsone; azotemia, pancreatitis, hypo- or hyperglycemia, leukopenia, electrolyte abnormalities, and cardiac dysrhythmia with pentamidine; anemia, rash, fever, and diarrhea with primaquine and clindamycin; headache, nausea, diarrhea, rash, and transaminase elevations with atovaquone.

IRIS has been reported following PCP. Most cases have occurred within weeks of the episode of PCP. Reported cases are not sufficient to provide guidance on the optimal time to start ART following a mild or severe case of PCP.

Management of Treatment Failure

Clinical failure is defined by the lack of improvement or worsening of respiratory function documented by arterial blood gases after at least 4 to 8 days of anti-PCP treatment. Treatment failure attributed to treatment-limiting toxicities occurs in up to one third of patients. Switching to another regimen is the appropriate management for treatment-related toxicity (**BII**). Failure attributed to lack of drug efficacy occurs in approximately 10% of those with mild-to-moderate disease. No convincing clinical trials exist to base recommendations for the management of treatment failure attributed to lack of drug efficacy. Clinicians should wait at least 4 to 8 days before switching therapy for lack of clinical improvement (**BIII**). In the absence of corticosteroid therapy, early and reversible deterioration within the first 3 to 5 days of therapy is typical, probably because of the inflammatory response caused by antibiotic-induced lysis of organisms in the lung. Other concomitant infections must be excluded as a cause for clinical failure; bronchoscopy with bronchoalveolar lavage should be strongly considered even if it was conducted before initiating therapy.

If TMP-SMX has failed or must be avoided for toxicity in moderate-to-severe disease, the common practice is to use parenteral pentamidine or primaquine combined with clindamycin (**BII**). For mild disease, atovaquone is a reasonable alternative (**BII**).

Preventing Recurrence

Patients who have a history of PCP should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with TMP-SMX unless immune reconstitution occurs as a result of ART (**AI**). For patients who are intolerant of TMP-SMX, alternatives are dapsone, dapsone combined with pyrimethamine, atovaquone, or aerosolized pentamidine.

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

Secondary prophylaxis should be discontinued for adult and adolescent patients whose $CD4^+$ count has increased from <200 cells/microliter to >200 cells/microliter for >3 months as a result of ART (**BII**).

If the episode of PCP occurred at a CD4+ count of >200 cells/microliter, continuing PCP prophylaxis for life, regardless of how high the CD4+ count rises as a consequence of ART, would be prudent (**CIII**); however, data regarding the most appropriate approach in this setting are limited.

Prophylaxis should be reintroduced if the $CD4^+$ T lymphocyte count decreases to <200 cells/microliter (**AIII**). If PCP recurs at a $CD4^+$ count of $\geq$200 cells/microliter, lifelong prophylaxis should be administered (**CIII**).

Special Considerations During Pregnancy

PCP diagnostic considerations for pregnant women are the same as for nonpregnant women. Indications for therapy are the same as for nonpregnant women. The preferred initial therapy during pregnancy is TMP-SMX, although alternate therapies can be used if patients are unable to tolerate or are unresponsive to TMP-SMX (**AI**).

Although first-trimester exposure to trimethoprim might be related to a small increased risk for birth defects, pregnant women in their first trimester with PCP should be treated with TMP-SMX (**AIII**). Although folic acid supplementation of 0.4 mg/day is routinely recommended for all pregnant women, data do not indicate if higher levels of supplementation, such as the 4 mg/day recommended for pregnant women with a previous infant with a neural tube defect, would provide added benefit in this situation. Follow-up ultrasound to assess fetal anatomy at 18 to 20 weeks is recommended (**BIII**).

Neonatal care providers should be informed of maternal sulfa or dapsone therapy if used near the delivery date because of the theoretical increased risk for hyperbilirubinemia and kernicterus.

Pentamidine is embryotoxic but not teratogenic among rats and rabbits. Adjunctive corticosteroid therapy should be used as indicated in nonpregnant adults (**AIII**). Maternal fasting and postprandial glucose levels should be monitored closely when corticosteroids are used in the third trimester because the risk for glucose intolerance is increased.

Rates of preterm labor and preterm delivery are increased with pneumonia during pregnancy. Pregnant women with pneumonia after 20 weeks of gestation should be monitored for evidence of contractions (**BII**).

Chemoprophylaxis for PCP should be administered to pregnant women the same as for other adults and adolescents (**AIII**). TMP-SMX is the recommended prophylactic agent; dapsone is an alternative. Because of theoretical concerns regarding possible teratogenicity associated with drug exposures during the first trimester, health-care providers might withhold prophylaxis during the first

trimester. In such cases, aerosolized pentamidine can be considered because of its lack of systemic absorption and the resultant lack of exposure of the developing embryo to the drug (**CIII**).

***Toxoplasma gondii* Encephalitis (TE)**

Preventing Exposure

HIV-infected persons should be tested for immunoglobulin G (IgG) antibody to *Toxoplasma* soon after the diagnosis of HIV infection to detect latent infection with *T. gondii* (**BIII**).

HIV-infected persons, including those who lack IgG antibody to *Toxoplasma*, should be counseled regarding sources of *Toxoplasma* infection. To minimize risk for acquiring toxoplasmosis, HIV-infected persons should be advised not to eat raw or undercooked meat, including undercooked lamb, beef, pork, or venison (**BIII**). Specifically, lamb, beef, venison, and pork should be cooked to an internal temperature of 165 degrees F to 170 degrees F; meat cooked until it is no longer pink inside usually has an internal temperature of 165 degrees F to 170 degrees F and therefore, from a more practical perspective, satisfies this requirement. To minimize the risk for acquiring toxoplasmosis, HIV-infected persons should wash their hands after contact with raw meat and after gardening or other contact with soil; in addition, they should wash fruits and vegetables well before eating them raw (**BIII**). If the patient owns a cat, the litter box should be changed daily, preferably by an HIV-negative, nonpregnant person; alternatively, patients should wash their hands thoroughly after changing the litter box (**BIII**). Patients should be encouraged to keep their cats inside and not to adopt or handle stray cats (**BIII**). Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats (**BIII**). Patients need not be advised to part with their cats or to have their cats tested for toxoplasmosis (**EII**).

Preventing Disease

Initiating Primary Prophylaxis

Toxoplasma-seropositive patients who have a CD4+ count of <100 cells/microliter should be administered prophylaxis against TE (**AII**). The double-strength tablet daily dose of TMP-SMX recommended as the preferred regimen for PCP prophylaxis also is effective against TE and is therefore recommended (**AII**). TMP-SMX, one double-strength tablet three times weekly, is an alternative (**BIII**). If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against PCP (**BI**). Atovaquone with or without pyrimethamine/leucovorin also can be considered (**CIII**). Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data (**DII**). Aerosolized pentamidine does not protect against TE and is not recommended (**EI**).

Toxoplasma-seronegative persons who are not taking a PCP prophylactic regimen known to be active against TE (e.g., aerosolized pentamidine) should be retested for IgG antibody to *Toxoplasma* when their CD4+ counts decline to <100 cells/microliter to determine whether they have seroconverted and are therefore

at risk for TE (**CIII**). Patients who have seroconverted should be administered prophylaxis for TE as described previously (**AII**).

Discontinuing Primary Prophylaxis

Prophylaxis against TE should be discontinued among adult and adolescent patients who have responded to ART with an increase in CD4+ counts to >200 cells/microliter for >3 months (**AI**).

Discontinuing primary TE prophylaxis is recommended because prophylaxis at CD4+ count >200 cells/microliter adds limited disease prevention for toxoplasmosis and because discontinuing drugs reduces pill burden, potential for drug toxicity, drug interaction, selection of drug-resistant pathogens, and cost. Prophylaxis for TE should be reintroduced if the CD4+ count decreases to <100 to 200 cells/microliter (**AIII**).

Treatment of Disease

The initial therapy of choice for TE consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin (**AI**).

The preferred alternative regimen for patients who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin (**AI**).

TMP-SMX was reported in a small (77 patients) randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with TMP-SMX, treatment with this drug may be considered an option (**BI**). For patients who cannot take an oral regimen, no well-studied options exist. No parenteral formulation of pyrimethamine exists; the only widely available parenteral sulfonamide is the sulfamethoxazole component of TMP-SMX. Certain specialists will treat severely ill patients initially requiring parenteral therapy for TE with parenteral TMP-SMX or oral pyrimethamine plus parenteral clindamycin (**CIII**).

The following regimens have been show to be effective in the treatment of TE in at least two, nonrandomized, uncontrolled trials, although their relative efficacy compared with the previous regimens is unknown: atovaquone (with meals or oral nutritional supplements) plus either pyrimethamine plus leucovorin or sulfadiazine or, for patients intolerant of both pyrimethamine and sulfadiazine, as a single agent (**BII**) (if atovaquone is used alone, clinicians should be aware that different patients experience a high variability of absorption of the drug; plasma levels of >18.5 micrograms/mL are associated with an improved response rate but measurements are not routinely available); and azithromycin plus pyrimethamine plus leucovorin daily (**BII**).

The following regimens have been reported to have activity in the treatment of TE in small cohorts of patients or in case reports of one or several patients: clarithromycin plus pyrimethamine (**CIII**); 5-fluorouracil plus clindamycin (**CIII**), dapsone plus pyrimethamine plus leucovorin (**CIII**); and minocycline or doxycycline combined with either pyrimethamine plus leucovorin, sulfadiazine, or

clarithromycin (**CIII**). Although the clarithromycin dose used in the only published study was 1 g twice a day, doses >500 mg have been associated with increased mortality in HIV-infected patients treated for disseminated *Mycobacterium avium* complex (MAC). Doses >500 mg twice a day should not be used (**DIII**).

Acute therapy for TE should be continued for at least 6 weeks, if there is clinical and radiologic improvement (**BII**). Longer courses might be appropriate if clinical or radiologic disease is extensive or response is incomplete at 6 weeks. Central nervous system (CNS) lesions must not have contrast enhancement on computed tomography/magnetic resonance imaging (CT/MRI). Adjunctive corticosteroids (e.g., dexamethasone) should be administered to patients with TE when clinically indicated only for treatment of a mass effect associated with focal lesions or associated edema (**BIII**). Because of the potential immunosuppressive effects of corticosteroids, they should be discontinued as soon as clinically feasible. Patients receiving corticosteroids should be monitored closely for the development of other OIs, including cytomegalovirus (CMV) retinitis and TB disease.

Anticonvulsants should be administered to patients with TE who have a history of seizures (**AIII**), but should not be administered as prophylactics to all patients (**DIII**). Anticonvulsants, if administered, should be continued at least through the period of acute therapy.

Monitoring and Adverse Events, Including IRIS

Changes in antibody titers are not useful for monitoring responses to therapy. Patients with TE should be monitored routinely for adverse events and clinical and radiologic improvement (**AIII**). Common pyrimethamine toxicities include rash, nausea, and bone-marrow suppression (neutropenia, anemia, and thrombocytopenia) that can often be reversed by increasing the dose of leucovorin to 50 to 100 mg/day administered in divided doses (**CIII**).

Common sulfadiazine toxicities include rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhea, and crystalluria. Common clindamycin toxicities include fever, rash, nausea, diarrhea (including pseudomembranous colitis or diarrhea related to *Clostridium difficile* toxin), and hepatotoxicity. Common TMP-SMX toxicities include rash, fever, leukopenia, thrombocytopenia, and hepatotoxicity. Drug interactions between anticonvulsants and antiretroviral agents should be carefully evaluated and doses adjusted according to established guidelines.

Several cases of neurologic disease have been attributed to immune reconstitution and toxoplasmosis, but more data are needed to verify that such cases are IRIS related to *T. gondii*.

Management of Treatment Failure

A brain biopsy, if not previously performed, should be strongly considered for patients who fail to respond to initial therapy for TE (**BII**) as defined by clinical or radiologic deterioration during the first week despite adequate therapy or lack of clinical improvement within 2 weeks. For those who undergo brain biopsy and have confirmed histopathologic evidence of TE, a switch to an alternative regimen as previously described should be considered (**BIII**). Recurrence of disease during

secondary maintenance therapy following an initial clinical and radiographic response is unusual if patients adhere to their regimen.

Preventing Recurrence

Patients who have completed initial therapy for TE should be administered lifelong suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) (**AI**) unless immune reconstitution occurs because of ART, in which case discontinuation of treatment is indicated. The combination of pyrimethamine plus sulfadiazine plus leucovorin is highly effective as suppressive therapy for patients with TE (**AI**) and provides protection against PCP (**AII**). Although sulfadiazine is routinely dosed as a four times a day regimen, a pharmacokinetic study suggests bioequivalence when using the same total daily dose in a twice a day or four times a day regimen, and limited clinical experience suggests that twice a day dosing is effective. A commonly used regimen as suppressive therapy for patients with TE who cannot tolerate sulfa drugs is pyrimethamine plus clindamycin (**BI**). Because of the high failure rate observed with lower doses, a dose of 600 mg clindamycin every 8 hours is recommended **(CIII)**. However, this regimen does not provide protection against PCP (**AII**), and thus an additional agent (e.g., aerosol pentamidine) must be used. Atovaquone with or without pyrimethamine or sulfadiazine is also active against both TE and PCP (**BII**) but is substantially more expensive. A small uncontrolled study in patients who had been receiving ART for a median of 13 months suggested that TMP-SMX could be used as a suppressive regimen to reduce pill burden.

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

Adult and adolescent patients receiving secondary prophylaxis (i.e., chronic maintenance therapy) for TE are at low risk for recurrence of TE when they have successfully completed initial therapy for TE, remain asymptomatic with regard to signs and symptoms of TE, and have a sustained increase in their $CD4^+$ counts of >200 cells/microliter after ART (e.g., >6 months). Although the numbers of patients who have been evaluated in observational studies and in one randomized clinical trial remain limited, and occasional recurrences have been reported, on the basis of these observations and inference from more extensive cumulative data indicating the safety of discontinuing secondary prophylaxis for other OIs during advanced HIV disease, discontinuing chronic maintenance therapy among such patients is a reasonable consideration (**BI**). Certain specialists recommend obtaining an MRI of the brain as part of their evaluation to determine whether discontinuing therapy is appropriate by assessing whether the brain lesions had resolved.

Secondary prophylaxis (chronic maintenance therapy) for TE should be reintroduced if the $CD4^+$ count decreases to <200 cells/microliter (**AIII**).

Special Considerations During Pregnancy

Documentation of maternal *Toxoplasma (T.) gondii* serologic status should be obtained during pregnancy. Indications for treatment of *T. gondii* during pregnancy should be based on confirmed or suspected symptomatic disease in the mother. Pediatric-care providers should be informed if the HIV-infected mother is seropositive for *T. gondii* infection to allow evaluation of the neonate for evidence

of congenital infection. Pregnant HIV-infected women with suspected or confirmed primary *T. gondii* infection during pregnancy should be managed in consultation with a maternal-fetal medicine or other appropriate specialist (**BIII**).

Treatment should be the same as in nonpregnant adults (**BIII**). Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk for defects and, therefore, it can be administered to pregnant women. Pediatric providers should be notified if sulfadiazine is continued until delivery because its use might increase the risk for neonatal hyperbilirubinemia and kernicterus.

Pregnant, HIV-infected women who have evidence of primary toxoplasmic infection or active toxoplasmosis, including TE, should be evaluated and managed during pregnancy in consultation with appropriate specialists (**BIII**). Because the risk for transmission with chronic infection appears low, routine evaluation of the fetus for infection with amniocentesis or cordocentesis is not indicated. Detailed ultrasound examination of the fetus specifically evaluating for hydrocephalus, cerebral calcifications, and growth restriction should be done for HIV-infected women with suspected primary or symptomatic reactivation of *T. gondii* during pregnancy.

TMP-SMX can be administered for primary prophylaxis against TE as described for PCP (**AIII**). Secondary prophylaxis should be provided using the same indications as for nonpregnant women. The risks of TMP-SMX in the first trimester, as discussed for PCP, must be balanced against the risk for recurrent TE.

Cryptosporidiosis

Preventing Exposure

HIV-infected persons should be educated and counseled concerning the different ways that *Cryptosporidium* can be transmitted (**BIII**).

Scrupulous handwashing can reduce the risk for diarrhea in HIV-infected persons, including diarrhea caused by *Cryptosporidium*. HIV-infected persons should be advised to wash their hands after potential contact with human feces (including after diapering small children) and after the following activities: handling pets or other animals, gardening or other contact with soil, before preparing food, before eating, and before and after sex (**BIII**). HIV-infected persons should avoid unprotected sex practices, especially practices that could lead to direct (e.g., oral-anal) or indirect (e.g., penile-anal) contact with feces. Patients should be advised to use barriers during sex to reduce such exposures (e.g., condoms, dental dams) (**BIII**).

HIV-infected persons (particularly those with CD4+ counts <200 cells/microliter), should avoid direct contact with diarrhea or stool from pets, particularly any stray pets, or dogs and cats aged <6 months (**BIII**). Gloves should be worn when handling feces or cleaning areas that might have been contaminated by feces from pets (**BIII**). HIV-infected persons should limit or avoid direct exposure to calves and lambs (e.g., farms, petting zoos) (**BII**).

HIV-infected persons should not drink water directly from lakes or rivers (**AIII**).

They should avoid swimming in water that is likely contaminated and should avoid swallowing water while swimming or playing in recreational water (**BIII**).

Outbreaks of cryptosporidiosis have been linked to drinking water from municipal water supplies. During outbreaks or in other situations that impose a community advisory to boil water, boiling water for at least 3 minutes will eliminate the risk for cryptosporidiosis (**AIII**). Using submicron personal-use water filters (home/office types) or bottled water might also reduce the risk for infection from municipal and well water (**CIII**).

HIV-infected persons should avoid eating raw oysters because cryptosporidial oocysts can survive in oysters for >2 months and have been found in oysters taken from certain commercial oyster beds (**BIII**). In a hospital, standard precautions (i.e., use of gloves and handwashing after removal of gloves) should be sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible HIV-infected person (**BIII**). However, because of the potential for fomite transmission, some specialists recommend that HIV-infected persons, specifically persons who are severely immunocompromised, should not share a room with a patient with cryptosporidiosis (**CIII**).

If HIV-infected persons travel in developing countries, they should be warned to avoid drinking tap water or using tap water to brush their teeth (**BIII**). Ice that is not made from bottled water also should be avoided. Raw fruits or vegetables that might have been washed in tap water also should be avoided (**BIII**). HIV-infected persons also should avoid other sources of *Cryptosporidium* oocytes as much as possible (**BIII**). These include working directly with people with diarrhea; with farm animals, cattle, and sheep; and with domestic pets that are very young or have diarrhea. If exposure is unavoidable, then the use of gloves and good hand hygiene is recommended.

Preventing Disease

Because chronic cryptosporidiosis occurs primarily in persons with advanced immunodeficiency, appropriate initiation of ART before the patient becomes severely immunosuppressed should prevent this disease (**AIII**). Rifabutin (RIF) or clarithromycin, when taken for MAC prophylaxis, have been found to protect against cryptosporidiosis. However, data are insufficient to warrant a recommendation for using rifabutin or clarithromycin as chemoprophylaxis for cryptosporidiosis.

Treatment of Disease

In the setting of severe immunosuppression, ART with immune restoration to a $CD4^+$ count >100 cells/microliter leads to resolution of cryptosporidiosis, and is the mainstay of treatment. Therefore, patients with cryptosporidiosis should be offered ART as part of the initial management of their infection (**AII**). Management should include symptomatic treatment of diarrhea (**AIII**). Rehydration and repletion of electrolyte losses by either the oral or IV route are important. Severe diarrhea can exceed >10 L/day among patients with AIDS,

often requiring intensive support. Oral rehydration should be pursued aggressively with oral rehydration solutions (**AIII**).

Multiple agents have been investigated in small randomized controlled clinical trials of HIV-infected adults, including nitazoxanide, paromomycin, spiramycin, bovine hyperimmune colostrum, and bovine dialyzable leukocyte extract. No pharmacologic or immunologic therapy directed specifically against *Cryptosporidium parvum* (*C. parvum*) has been shown to be consistently effective when used without ART.

Nitazoxanide is an orally administered nitrothiazole benzamide with in vivo activity against a broad range of helminths, bacteria, and protozoa. Because of the clinical significance of cryptosporidiosis, a trial of nitazoxanide in conjunction with ART, but never instead of ART, may be considered (**CIII**).

Data do not support a recommendation for the use of paromomycin for cryptosporidiosis (**DII**).

Treatment with antimotility agents (e.g., loperamide, tincture of opium) can palliate symptoms by reducing diarrheal frequency and volume, but these agents are not consistently effective (**BIII**). Octreotide, a synthetic octapeptide analog of naturally occurring somatostatin that is approved for the treatment of secreting tumor-induced diarrhea, is no more effective than other oral antidiarrheal agents, and is usually not recommended (**DII**).

Monitoring and Adverse Events, Including IRIS

Patients should be monitored closely for signs and symptoms of volume depletion, electrolyte and weight loss, and malnutrition. Total parenteral nutrition might be indicated in certain patients (**CIII**).

IRIS has not been described in association with treatment of cryptosporidiosis.

Management of Treatment Failure

Supportive treatment and optimizing ART to achieve full virologic suppression are the only feasible approaches to the management of treatment failure (**AIII**).

Preventing Recurrence

No pharmacologic interventions are known to be effective in preventing the recurrence of cryptosporidiosis.

Special Considerations During Pregnancy

As with nonpregnant woman, initial treatment should rely on rehydration and initiation of ART (**AII**). Pregnancy should not preclude the use of ART. Nitazoxanide is not teratogenic in animals but human data on use in pregnancy are not available. Nitazoxanide may be used in pregnancy after the first trimester in severely symptomatic pregnant women (**CIII**).

Microsporidiosis

Preventing Exposure

Patients with AIDS (e.g., CD4+ count <200 cells/microliter) should avoid untreated water sources (**AIII**). Otherwise, other than general attention to handwashing and other personal hygiene measures, no precautions to reduce exposure to microsporidia are recommended.

Preventing Disease

No chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Treatment of Disease

ART with immune restoration (an increase of $CD4^+$ count to >100 cells/microliter) is associated with resolution of symptoms of enteric microsporidiosis, including that caused by *Enterocytozoon (E.) bieneusi*. All patients should be offered ART as part of the initial management of microsporidial infection (**AII**).

No specific therapeutic agent is active against *E. bieneusi* infection. A controlled clinical trial suggested that *E. bieneusi* might respond to oral fumagillin (60 mg/day), a water insoluble antibiotic made by *Aspergillus fumigatus* (**BII**), or to its synthetic analog TNP-470 (**BIII**). However, fumagillin and TNP-470 are not available for systemic use in the United States. One report indicated that treatment with nitazoxanide for 60 days might resolve chronic diarrhea caused by *E. bieneusi* in the absence of ART; however, the effect appeared to be minimal among patients with low $CD4^+$ counts. Therefore, this drug cannot be recommended with confidence (**CIII**).

Albendazole is recommended for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *Enterocytozoon (E.) bieneusi* and *Vittaforma (V.) corneae* (**AII**).

Itraconazole might be useful in disseminated disease when combined with albendazole, especially in infections caused by *Trachipleistophora* or *Anncaliia* (**CIII**).

Ocular infections caused by microsporidia should be treated with topical Fumidil B (fumagillin bicyclohexylammonium) in saline (to achieve a concentration of 70 micrograms/mL of fumagillin) (**BII**). Topical fumagillin is the only formulation available for treatment in the United States and is investigational. Although clearance of microsporidia from the eye can be demonstrated, the organism often is still present systemically and can be detected in the urine or in nasal smears. In such cases, the use of albendazole as a companion systemic agent to fumagillin is recommended in ocular infections (**BIII**).

Metronidazole and atovaquone are not active *in vitro* or in animal models and should not be used to treat microsporidiosis (**DII**). Fluid support should be offered if diarrhea has resulted in dehydration (**AIII**). Patients with malnutrition and

wasting should be treated with nutritional supplementation (**AIII**). Antimotility agents can be used if required for diarrhea control (**BIII**).

Monitoring and Adverse Events, Including IRIS

Albendazole side effects are rare but hypersensitivity (rash, pruritis, fever), neutropenia (reversible), CNS effects (dizziness, headache), gastrointestinal disturbances (abdominal pain, diarrhea, nausea, vomiting), hair loss (reversible), and elevated hepatic enzymes (reversible) have been reported. Albendazole is not carcinogenic or mutagenic. Topical fumagillin has not been associated with substantial side effects. Oral fumagillin has been associated with thrombocytopenia, which is reversible on stopping the drug.

An IRIS has not been described in association with treatment for *E. bieneusi* or non-*E. bieneusi* microsporidiosis.

Management of Treatment Failure

Supportive treatment and optimizing ART to attempt to achieve full virologic suppression are the only feasible approaches to the management of treatment failure (**AIII**).

Preventing Recurrence

Treatment for ocular microsporidiosis should be continued indefinitely because recurrence or relapse might follow treatment discontinuation (**BIII**). Whether treatment of other manifestations can be safely discontinued after immune restoration with ART is unknown; however, such a practice is reasonable, based on experience with discontinuation of secondary prophylaxis (chronic maintenance therapy) for other OIs present during advanced HIV disease. Therefore, certain specialists recommend discontinuing chronic maintenance therapy if patients no longer have signs and symptoms of microsporidiosis and have a sustained (e.g., >6 months) increase in their $CD4^+$ counts to levels >200 cells/microliter after ART (**BIII**).

Special Considerations During Pregnancy

The primary approach to treatment of microsporidiosis in pregnancy should be initiation of ART to restore immune function. Among animals (i.e., rats and rabbits), albendazole is embryotoxic and teratogenic at dosages of 20 mg/kg body weight. Therefore, albendazole is not recommended for use among pregnant women (**DIII**). However, well-controlled studies in human pregnancy have not been performed. Systemic fumagillin has been associated with increased resorption and growth retardation in rats. No data on use in human pregnancy are available. However, because of the antiangiogenic effect of fumagillin, this drug should not be used among pregnant women (**EIII**). Topical fumagillin has not been associated with embryotoxic or teratogenic effects among pregnant women and might be considered when therapy with this agent is appropriate (**CIII**).

Mycobacterium tuberculosis **Infection and Disease**

Preventing Exposure

HIV-infected persons should be advised that time spent in congregate settings or other environments identified as possible sites of TB transmission (e.g., correctional facilities, homeless shelters, nursing homes) might increase the likelihood of contracting *M. tuberculosis* infection (**BIII**).

In health-care facilities and other environments with a high risk for transmission, all patients with known or presumed infectious TB should be physically separated from other patients, but especially from those with HIV infection (**AII**). A patient with infectious TB returning to a congregate living setting or to any setting in which susceptible persons might be exposed should be receiving or should have completed treatment and have three consecutive negative AFB smear results from good quality sputum samples collected $\geq$8 hours apart (with one specimen collected during the early morning), be on adequate treatment for >2 weeks, and demonstrate clinical improvement before being considered noninfectious (**AIII**). Certain specialists recommend that patients with multidrug resistant (MDR)-TB have a negative sputum culture before returning to a congregate setting.

Treatment of latent TB infection (LTBI) is effective in reducing TB incidence among populations who reside in areas of low, medium, and high TB transmission. All possible strategies should be pursued to ensure that HIV-infected persons with risk factors for TB are tested for *M. tuberculosis* infection and those with LTBI receive and complete a course of LTBI treatment (**AII**). Persons infected with HIV should be treated presumptively for LTBI when the history of TB exposure is substantial, regardless of the results of diagnostic testing for LTBI (**BII**). Use of Bacillus Calmette-Guérin (BCG) vaccine is not recommended as a means to control TB in the U.S. because of the unproven efficacy of the vaccine in the U.S. population and the success of other measures in reducing TB incidence. BCG vaccination for HIV-infected persons is contraindicated because of its potential to cause disseminated disease (**EII**).

Preventing Disease (Treatment of LTBI)

All HIV-infected persons with suspected LTBI or who have symptoms indicating TB should promptly undergo chest radiography and clinical evaluation to rule out active TB regardless of the results of diagnostic tests for LTBI.

HIV-infected persons, regardless of age, should be treated for LTBI if they have no evidence of active TB and exhibit the following characteristics: 1) a positive diagnostic test for LTBI and no prior history of treatment for active or latent TB (**AI**); 2) a negative diagnostic test for LTBI but are close contacts of persons with infectious pulmonary TB (**AII**); and 3) a history of untreated or inadequately treated healed TB (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for LTBI (**AII**).

The efficacy of LTBI treatment has not been documented for HIV-infected persons with negative diagnostic tests for LTBI without known exposure to *M. tuberculosis*. Persons from groups or geographic areas with a high prevalence of *M. tuberculosis* infection might be at increased risk for primary or reactivation TB and, in this situation, decisions to treat for LTBI must include consideration of CD4+ count and other factors (**BIII**).

Treatment options for LTBI include isoniazid (INH) daily (**AII**) or twice weekly (**BII**) for 9 months.

Because of an increased risk for fatal and severe hepatotoxicity, a 2-month regimen of daily rifampin (RIF) and pyrazinamide (PZA) is not recommended for LTBI treatment regardless of HIV status (**DI**). HIV-infected persons receiving INH should receive pyridoxine (**BIII**) to minimize the risk for developing peripheral neuropathy. Alternatives for persons who cannot take INH or who have been exposed to a known INH-resistant index patient include either RIF or rifabutin alone for 4 months (**BIII**). Decisions to use a regimen containing either RIF or rifabutin should be made after considering potential drug interactions (see the section on ART in the Management of TB Disease). For persons exposed to INH- and/or RIF-resistant TB, decisions to treat with one or two drugs other than INH, RIF, or rifabutin should be based on the relative risk for exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities (**AII**). Directly observed therapy (DOT) should be used with intermittent dosing regimens (**AI**) when otherwise feasible to maximize regimen-completion rates.

No evidence suggests that LTBI treatment should be continued beyond the recommended duration in persons with HIV infection. Therefore, LTBI treatment should be discontinued after completing the appropriate number of doses (**AII**)

Treatment of Disease

Considering the variability of yield from smear microscopy and nucleic acid amplification tests, empiric treatment should be initiated and continued in HIV-infected persons in whom TB is suspected until all diagnostic work-up (smears, cultures, or other identification results) is complete (**AII**). When active TB is diagnosed or suspected, a multi-drug anti-TB treatment regimen should be started immediately (**AI**). This approach promotes rapid killing of tubercle bacilli, prevents the emergence of drug resistance, and decreases the period of contagion. DOT is recommended for all patients with HIV-related TB (**AII**). Likelihood of treatment success is further enhanced by DOT with support for other social and medical needs of HIV-infected patients (**BII**) (enhanced DOT). A treatment plan should be based on completion of the total number of recommended doses ingested rather than the duration of treatment administration (**AIII**). The following text summarizes both duration-based and total number-based dosing recommendations.

Recommendations for anti-TB treatment regimens in HIV-infected adults follow the same principles as for adults without HIV-infection (**AI**). Treatment of drug susceptible TB disease should include a 6-month regimen with an initial phase of INH, RIF or rifabutin, pyrazinamide (PZA), and ethambutol (EMB) administered for 2 months followed by INH and RIF (or rifabutin) for 4 additional months (**AI**). When drug-susceptibility testing confirms the absence of resistance to INH, RIF, and PZA, EMB may be discontinued before 2 months of treatment have been completed (**AI**). For patients with cavitary lung disease and cultures positive for *M. tuberculosis* after completion of 2 months of therapy, treatment should be extended with INH and RIF for an additional 3 months for a total of 9 months (**AII**). All HIV-infected patients treated with INH should receive pyridoxine supplementation (**BIII**). For patients with extrapulmonary TB, a 6- to 9-month

regimen (2 months of INH, RIF, PZA, and EMB followed by 4 to 7 months of INH and RIF) is recommended (**AII**). Exceptions to the recommendation for a 6- to 9-month regimen for extrapulmonary TB include CNS disease (tuberculoma or meningitis) and bone and joint TB, for which many experts recommend 9 to 12 months (**AII**). Adjuvant corticosteroids should be added when treating CNS and pericardial disease (**AII**). Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement (see Table 3 in the original guideline document). Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over 6 to 8 weeks or prednisone 1 mg/kg for 3 weeks, then tapered for 3 to 5 weeks.

The optimal way to prevent relapse has not been determined. How the CD4+ count relates to likelihood of treatment failure and relapse remains uncertain. Some recent observational studies suggest that 9 months of therapy result in a lower rate of relapse than shorter or 6-month anti-TB regimens. While awaiting definitive results of randomized comparisons of treatment duration in HIV-infected patients with TB disease, 6 months of therapy are probably adequate for the majority of patients, but prolonged therapy (up to 9 months) is recommended (as in HIV-negative patients) for patients with a delayed response to therapy, with cavitary disease on chest radiograph, and for those with extrapulmonary or CNS disease (**BII**).

Intermittent dosing (twice- or thrice- weekly) facilitates DOT by decreasing the total number of encounters required, might provide more effective peak serum concentrations, and is preferable to complete the regimen. For HIV-infected patients, the initial 8-week phase of therapy should be administered daily by DOT (7 days per week for 56 doses or 5 days per week for 40 doses) (**AII**) or 3 times weekly by DOT for 24 doses (**BII**). Because twice-weekly administration of the continuation phase of therapy is associated with an increased risk for relapse with acquired rifamycin-resistant *M. tuberculosis* strains, for patients with CD4+ counts <100 cells/microliter the continuation phase of either 4 months or 7 months should be administered either daily or three times weekly by DOT (**AIII**). Twice-weekly continuation-phase therapy may be considered in patients with CD4+ counts $\geq$100 cells/microliter (**CIII**). Once-weekly administration of INH-rifapentine in the continuation phase should not be used for any patient with HIV infection (**EI**).

Monitoring and Adverse Events, Including IRIS

Monitoring of LTBI Treatment

All patients with a diagnosis of LTBI should be counseled about risk for TB, adherence to treatment regimens, benefits and risks of treatment, interactions with other drugs, and an optimal follow-up plan. HIV-infected patients receiving treatment for LTBI also should have baseline laboratory testing, including an evaluation of hepatic function (serum aspartate aminotransferase [AST], bilirubin, and alkaline phosphatase) for patients treated with INH and a complete blood count and platelet count for patients taking RIF or rifabutin.

Patients being treated for LTBI should be monitored at least monthly with a history and physical assessment designed to detect hepatitis and neuropathy.

Patients should be advised to stop treatment and promptly seek medical evaluation if symptoms suggesting hepatitis occur, such as nausea, vomiting, jaundice, or dark urine. Clinicians in all settings should consider dispensing no more than a 1-month supply of medication. Routine laboratory monitoring is indicated in HIV-infected patients with abnormal baseline liver-function tests, with chronic liver disease, or in those receiving treatment with ART.

Monitoring of Active TB Disease Treatment

A baseline evaluation and monthly follow-up consisting of clinical, bacteriologic, and periodic laboratory and radiographic evaluations are essential to ensure treatment success. Clinical history and baseline tests to evaluate hepatic function (AST, bilirubin, and alkaline phosphatase), renal function (serum creatinine), complete blood count (including platelet count), and CD4+ counts are recommended for all patients. HIV-infected patients being treated for active TB should have a clinic-based evaluation at least monthly. For patients with extrapulmonary TB, the frequency and types of evaluations will depend on the sites involved and the ease with which specimens can be obtained. For patients with pulmonary TB, at least one sputum specimen for AFB smear and mycobacterial culture should be obtained monthly until two consecutive specimens are culture negative. Sputum specimens should be obtained after 8 weeks of treatment to inform clinical decision-making about the duration of the continuation phase. For patients with positive AFB smears at initiation of treatment, follow-up smears may be obtained at more frequent intervals (e.g., every 2 weeks until two consecutive specimens are negative) to provide an early assessment of the treatment response.

For patients with positive *M. tuberculosis* cultures after 3 months of treatment, drug-susceptibility tests should be repeated on newly acquired sputum specimens. Patients with positive *M. tuberculosis* cultures after 4 months of treatment should be considered as treatment failures and managed accordingly. At each visit, patients should be questioned about adherence and possible adverse effects of anti-TB medications; those taking EMB should be asked about blurred vision or scotomata and tested for visual acuity and color discrimination. Routine laboratory monitoring during treatment, even when baseline laboratory abnormalities are not present, could be considered.

In HIV-infected persons with active TB, serum concentrations of the first-line anti-TB drugs are frequently lower than published normal ranges. However, routine drug-level monitoring is not recommended. For those with a slow response to treatment, drug concentration measurements might provide objective information on which to base modifications of treatment.

Management of Common Adverse Events

Although the reported frequency of anti-TB drug-related toxicity in patients with HIV infection varies, for most adverse events, rates are not different than for HIV-uninfected patients. Because alternative drugs often have less efficacy and more toxicities than first-line anti-TB drugs and diagnosing a drug reaction and determining the responsible agent can be difficult, the first-line drugs (especially INH, RIF, or rifabutin) should not be stopped permanently without strong evidence that the specific anti-TB drug was the cause of the reaction. In such

situations, consultation with a specialist in treating LTBI or TB in persons with HIV infection is recommended.

Gastrointestinal reactions are common with many of the anti-TB medications. If gastrointestinal symptoms occur, AST and bilirubin should be measured, and if the AST level is less than three times the upper limit of normal (ULN) or the baseline for the patient, the symptoms are assumed not to be caused by hepatic toxicity. Typically, gastrointestinal symptoms should be managed without discontinuing TB medications; initial approaches should include either changing the hour of administration or administering drugs with food.

Skin rashes are common with all of the anti-TB drugs. If rash is minor, affects a limited area, or causes pruritis, antihistamines should be administered for symptomatic relief and all anti-TB medications continued. If the rash is severe, all TB medications should be stopped until the rash is substantially improved, and TB drugs restarted one by one at intervals of 2 to 3 days. RIF or rifabutin should be restarted first (because they are least likely to cause rash and their role in treatment is critical). If the rash recurs, the last drug added should be stopped. If a petechial rash thought to be caused by thrombocytopenia occurs, the RIF or rifabutin should be stopped permanently. If a generalized rash associated with either fever or mucous membrane involvement occurs, all drugs should be stopped immediately, the patient should be switched to alternative anti-TB agents, and LTBI or TB treatment should be managed in consultation with a specialist.

Fever in an HIV-infected patient who has been receiving effective TB therapy for several weeks might represent drug fever, a paradoxical reaction, or IRIS. If superinfection or worsening TB is excluded as a potential cause, all TB drugs should be stopped. Once the fever has resolved, the general guidelines described for restarting/stopping drugs in the presence of a rash should be followed.

An increase in AST concentration occurs in approximately 20% of patients treated with the standard four-drug anti-TB regimen. Drug-induced liver injury can be caused by INH, rifamycins, or PZA and is defined as an AST elevation to $\geq$3 times the ULN in the presence of symptoms, or >5 times the ULN in the absence of symptoms. In addition to AST elevation, disproportionate increases in bilirubin and alkaline phosphatase occur occasionally. This latter pattern is more consistent with rifamycin hepatotoxicity than with INH or PZA hepatotoxicity. In most patients, asymptomatic aminotransferase elevations resolve spontaneously.

In the absence of symptoms, elevations of AST <3 times ULN should not prompt changes of TB therapy, but the frequency of clinical and laboratory monitoring should be increased. If AST levels are $\geq$5 times the ULN regardless of symptoms, >3 times the ULN with symptoms, or if a significant increase in bilirubin and/or alkaline phosphatase occurs, hepatotoxic drugs should be stopped, and the patient should be evaluated immediately. For any substantial new transaminase or bilirubin elevation, serologic testing for hepatitis A, B, and C should be performed and the patient questioned regarding symptoms suggestive of biliary tract disease and exposures to alcohol and other hepatotoxins.

If anti-TB drugs must be stopped for hepatotoxicity, substituting $\geq$3 nonhepatotoxic anti-TB drugs is prudent until the specific cause of hepatotoxicity

can be determined and an alternative longer-term regimen constructed. The suspected anti-TB medications should be restarted one at a time after the AST level returns to <2 times the ULN or to near baseline for patients with pre-existing abnormalities. Because the rifamycins are a critical part of the TB regimen and are less likely to cause hepatotoxicity than INH or PZA, they should be restarted first. If no increase in AST occurs after 1 week, INH may be restarted. PZA may be restarted 1 week after INH if AST does not increase. If symptoms recur or AST increases, the last drug added should be stopped. If RIF and INH are tolerated and hepatitis was severe, PZA should be assumed responsible and should be discontinued. In this last circumstance, depending on the number of doses of PZA taken, severity of disease, and bacteriological status, therapy might be extended to 9 months with RIF and INH alone.

For HIV-infected patients on LTBI therapy who have hepatotoxicity, most of the general guidelines described for restarting/stopping drugs for patients on therapy for active TB apply. The ultimate decision regarding resumption of therapy with the same or a different agent for LTBI treatment should be made after weighing the risk for additional hepatic injury against the benefit of preventing progression to TB disease and always in consultation with an expert in treating LTBI in persons with HIV infection.

ART in the Management of TB Disease

The treatment of TB can be complicated by drug interactions with the rifamycins and overlapping toxicities associated with antiretrovirals (ARVs) and anti-TB drugs when therapy for both HIV and TB infections is concomitantly administered. Both RIF and rifabutin induce cytochrome P450 3A (CYP3A) enzymes, and although rifabutin is not as potent an inducer as RIF, it is a substrate, leading to drug interactions with the protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) when these agents are concomitantly administered with the rifamycins; such administration might result in increased metabolism and suboptimal levels of ARVs.

Compared with PI-based regimens, NNRTI-based regimens have fewer interactions with RIF-based TB therapy. Rifabutin is an alternative to RIF and can be administered with PIs or NNRTIs with appropriate dose adjustments. Concomitant use of RIF with ritonavir-boosted PIs has been shown to result in subtherapeutic levels of the PI. Use of ritonavir-boosted saquinavir with RIF was associated with a high incidence of hepatotoxicity in a pharmacokinetic study using healthy volunteers. RIF should not be used in patients on PI-based regimens, with or without ritonavir-boosting (**EII**). For patients undergoing treatment for active TB, starting ART with either an efavirenz- or nevirapine-based regimen is preferred because these NNRTIs have fewer interactions with RIF (**BII**); dosage adjustments for these NNRTIs might be needed for persons weighing more than 60 kg (**BII**). Delavirdine should not be used with either RIF or rifabutin.

If rifabutin is used in place of RIF, dosage reduction is required with boosted-PI regimens. Efavirenz decreases the levels of rifabutin, and the dose of the latter might have to be increased. Nevirapine does not affect the levels of rifabutin sufficiently to merit adjustment of the rifabutin dose. Underdosing of ARVs or rifabutin can result in selection of HIV drug-resistant mutants or acquired

rifamycin resistance, respectively, whereas overdosing of rifabutin might result in dose-related toxicities such as neutropenia and uveitis. Because interpatient variations in the degree of enzyme induction or inhibition can occur, the use of therapeutic drug monitoring for levels of rifabutin, PIs, or NNRTIs might help to adjust dosing for individual patients.

HIV nucleos(t)ide analogs and the fusion inhibitor enfuvirtide are not affected by the CYP enzymes and can be used with the rifamycins. Results of ongoing drug-drug interaction studies predict that the combination of RIF (and possibly rifabutin) will result in decreased levels of maraviroc, raltegravir, and elvitegravir. Until data are available to guide dose adjustment, these drugs in combination should be avoided or used with extreme caution. Available NNRTIs and PIs do not have clinically significant drug interactions with other first- and second-line anti-TB drugs; thus, when rifamycins cannot be administered because of toxicity or resistance (MDR or extensively drug-resistant (XDR) *M. tuberculosis* strains), ART regimens should be selected on the basis of other factors appropriate to the patient (**AIII**).

Optimal Timing of Initiation of ART in ART-Naïve Patients with Active TB

For ART-naïve, HIV-infected persons who are diagnosed with active TB, anti-TB treatment must be started immediately (**AIII**). The optimal timing of initiation of ART in this setting is not clear. Options include simultaneous TB and ART or treatment of TB first with delay of ART by several weeks to months. A positive aspect of starting both regimens simultaneously is the possible prevention of progressive HIV disease and reduction in morbidity or mortality associated with TB or other OIs. A negative of this approach is the possibility of overlapping toxicities, drug interactions, a high pill burden, and the possibility of developing IRIS or a paradoxical reaction. These factors must be weighed carefully when choosing the best time to start ART in individual patients.

Several randomized clinical trials are under way to address the optimal timing of initiation of ART in persons being treated for active TB, but the results will not be known for several years. Pending these results, certain specialists determine when to start ART based on the immunologic status of the patients. For patients with a CD4+ count <100 cells/microliter, ART should be started after $\geq$2 weeks of TB treatment (**BII**) to reduce confusion about overlapping toxicities, drug interactions, and the occurrence of paradoxical reactions or IRIS. For persons with a CD4+ count of 100–200 cells/microliter, certain specialists would delay ART until the end of the 2-month intensive phase of anti-TB treatment (**BII**). In those with a sustained CD4+ count >200 cells/microliter, ART could be started during the anti-TB maintenance phase and for those with a CD4+ count >350 cells/microliter, after finishing anti-TB treatment (**BII**).

When TB occurs in patients already on ART, treatment for TB must be started immediately (**AIII**), and ART should be modified to reduce the risk for drug interactions and maintain virologic suppression. When TB occurs in the setting of virologic failure, ART drug-resistance testing should be performed and a new ART regimen constructed to achieve virologic suppression and avoid drug interactions with the anti-TB regimen administered (**AIII**).

Immune Reconstitution and Paradoxical Reactions

IRIS or paradoxical reactions are usually self-limited but if symptoms are severe, supportive treatment might be required, depending on the nature of the complications. Typically, a paradoxical or IRIS reaction that is not severe should be treated symptomatically with nonsteroidal anti-inflammatory agents without a change in anti-TB treatment or ART (**BIII**). Approaches to the management of severe reactions (e.g., high fever, airway compromise from enlarging lymph nodes, enlarging serosal fluid collections, increased intracranial pressure [ICP], or sepsis syndrome) have not been studied but might require invasive interventions such as surgical decompression, and although no specific treatment is recommended for severe reactions, improvement has been observed with the use of prednisone or methylprednisolone used at a dose of approximately 1 mg/kg body weight gradually reduced after 1 to 2 weeks (**BIII**).

Management of Treatment Failure

Drug-resistant TB continues to be a substantial clinical and public health problem. Predisposing factors include cavitary disease with a large bacillary load, use of an inadequate drug regimen, or a combined failure of both the patient and the provider to ensure compliance with the prescribed regimen. Ongoing transmission of drug-resistant strains is a source of new drug-resistant cases. The recommended treatment for drug-resistant TB is the same for HIV-infected as for non-HIV-infected patients (**AII**). The optimal duration of treatment for highly resistant strains has not been established.

For patients with *M. tuberculosis* strains resistant to INH, INH should be discontinued and the patient treated with a 6-month regimen of RIF, PZA, and EMB, which is nearly as effective as the conventional INH-containing regimen (**BII**). A fluoroquinolone may be added for those with more severe or extensive disease (**CIII**). Alternatively, treatment with RIF and EMB for 12 months can be used, with PZA added during at least the initial 2 months (**BII**).

Treatment regimens for TB disease caused by RIF monoresistant strains are less effective, and patients infected with these strains are at increased risk for relapse and treatment failure. A minimum of 12 to 18 months of treatment with INH, EMB, and a fluoroquinolone (e.g., levofloxacin, moxifloxacin) with PZA administered during the first 2 months is recommended (**BIII**). An injectable agent (e.g., amikacin or capreomycin) might be included in the first 2-3 months for patients with RIF mono-resistance and severe or extensive disease (**CIII**).

Patients with *M. tuberculosis* resistant to both INH and RIF (MDR-TB) are at high risk for treatment failure and further acquired resistance and require especially close follow-up during and after treatment. Treatment regimens for MDR-TB should be individualized, based on drug resistance test results, relative activities of available anti-TB agents, the extent of disease, potential interaction with ARVs, and presence of other comorbid conditions (**AIII**). Treatment regimens should consist of at least four effective drugs (**AIII**). The management of MDR-TB is complex and should be undertaken only by an experienced specialist or in close consultation with specialized treatment centers (**AIII**).

The WHO Emergency Global Task Force on XDR-TB has defined XDR-TB as resistance to at least INH and RIF among the first-line anti-TB drugs, and resistance to any fluoroquinolone and at least one of three injectable second-line

drugs (kanamycin, amikacin, capreomycin). Patients with *M. tuberculosis* resistant to RIF or any two first-line drugs should be tested for susceptibility to a full panel of anti-TB drugs (**BIII**). Repeat drug-susceptibility testing should be considered for HIV-infected patients with MDR-TB who are not responding to treatment to rapidly identify drug resistance that occurs during treatment (**BIII**). Contact investigation and strict infection-control precautions should be implemented according to national guidelines (**BIII**). The management of XDR-TB should be undertaken only by an experienced specialist in close consultation with specialized treatment centers (**AIII**).

Preventing Recurrence

For patients with a low ongoing risk for exposure and transmission of *M. tuberculosis* infection, chronic suppressive therapy after successful completion of a recommended treatment regimen for LTBI or active TB is unnecessary (**DII**). However, recurrence of TB disease can result from either endogenous relapse or exogenous reinfection.

Recent immigrants might be at high risk for recent infection or reinfection in their countries of origin. Close monitoring of recent immigrants at such risk is necessary.

Special Considerations During Pregnancy

HIV-infected pregnant women who do not have documentation of a negative TST result during the preceding year should be tested during pregnancy. The frequency of anergy is not increased during pregnancy, and routine anergy testing for HIV-infected pregnant women is not recommended. No data are available on the performance of the IGRAs for diagnosis of LTBI in pregnant women.

The diagnostic evaluation for TB disease in pregnant women is the same as for nonpregnant adults. Chest radiographs with abdominal shielding result in minimal fetal radiation exposure. An increase in pregnancy complications and undesirable outcomes (including preterm birth) and intrauterine growth retardation might be observed among pregnant women with either pulmonary or extrapulmonary TB not confined to the lymph nodes, especially when treatment is not begun until late in pregnancy.

Treatment of TB disease during pregnancy should be the same as for the nonpregnant women, but with attention given to the following considerations (**BIII**):

- Although INH is not teratogenic in animals or humans, hepatotoxicity caused by INH might occur more frequently in pregnancy and the postpartum period. Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended (**CIII**).
- RIF is not teratogenic in humans. Because of a potential increased risk for RIF-related hemorrhagic disease among neonates born to women who receive anti-TB therapy during pregnancy, prophylactic vitamin K, in a single 10 mg dose, should be administered to the neonate (**BIII**).
- PZA is not teratogenic among animals. Experience is limited with use in human pregnancy. Although World Health Organization (WHO) and the

International Union Against Tuberculosis and Lung Diseases have made recommendations for the routine use of PZA in pregnant women, it has not been recommended for general use during pregnancy in the US because data characterizing its effects in this setting are limited. If PZA is not included in the initial treatment regimen, the minimum duration of therapy should be 9 months. The decision regarding whether to include PZA for treatment should be made after consultation among obstetricians, TB specialists, and women, taking into account gestational age and likely susceptibility pattern of the infecting strain (**CIII**).

- EMB is teratogenic among rodents and rabbits at doses that are much higher than those used among humans. No evidence of teratogenicity has been observed among humans. Ocular toxicity has been reported among adults taking EMB, but changes in visual acuity have not been detected in infants born after exposure in utero.

Experience during pregnancy with using the majority of the second-line drugs for TB during pregnancy is limited. MDR-TB in pregnancy should be managed in consultation with a specialist. Therapy should not be withheld because of pregnancy (**AIII**). The following concerns should be considered when selecting second-line anti-TB drugs for use among pregnant women:

- Streptomycin use has been associated with a 10% rate of VIII nerve toxicity in infants exposed in utero; its use during pregnancy should be avoided if possible (**DIII**).
- Hearing loss has been detected in approximately 2% of children exposed to long-term kanamycin therapy in utero; like streptomycin, this agent should generally be avoided if possible (**DIII**). The fetus is at a theoretical risk of ototoxicity with in utero exposure to amikacin and capreomycin, but this risk has not been documented, and these drugs might be alternatives when an aminoglycoside is required for treatment of MDR-TB (**CIII**).
- Because arthropathy has been noted in immature animals exposed in utero to quinolones, quinolones are typically not recommended in pregnancy and among children aged <18 years (**CIII**). However, >400 cases of quinolone use in human pregnancies have been reported to various pregnancy registries, and use has not been associated with arthropathy or birth defects after in utero exposure. Thus, quinolones can be used in pregnancy for drug-resistant TB, if they are required on the basis of susceptibility testing (**CIII**).
- Para-aminosalicylic acid (PAS) is not teratogenic among rats or rabbits. In one study, a possible increase in limb and ear anomalies was reported among 143 infants delivered by women who were exposed during the first trimester of their pregnancies. No specific pattern of defects and no increase in rate of defects have been detected among subjects in other human studies, indicating that this agent can be used with caution if needed (**CIII**).
- Ethionamide has been associated with an increased risk for several anomalies among mice, rats, and rabbits after high dose exposure; no increased risk for defects was noted with doses similar to those used among humans, but experience is limited with use during human pregnancy. Thus, ethionamide should be avoided unless its use is necessary (**CIII**).
- No data are available from animal studies or reports of cycloserine use in humans during pregnancy.

If LTBI is diagnosed during pregnancy and active TB has been ruled out, treatment should be initiated during pregnancy whenever possible (**BIII**). If the woman is receiving ART only for prophylaxis of perinatal HIV transmission and will stop ARVs after delivery, deferral of treatment for LTBI until after delivery or use of a triple nucleoside regimen to allow use of RIF is reasonable. For women who require long-term ART for their own health, initiation of INH prophylaxis during pregnancy is recommended (**BIII**).

ART is indicated for all pregnant women either for treatment of maternal infection, or if not indicated for maternal therapy, for prevention of perinatal transmission of HIV. Pregnant women on ART who have a diagnosis of active TB should have their ARV regimens adjusted as needed to accommodate their TB drugs. For women whose diagnosis includes concurrent active TB and HIV infection during pregnancy, TB therapy should be initiated immediately and ART should be initiated as soon as possible thereafter, usually according to the principles described for nonpregnant adults. Efavirenz use is not recommended during the first trimester because of 1) substantial CNS and cleft defects seen in cynomolgus monkeys treated in the first trimester with efavirenz at doses similar to those used in humans and 2) because of case reports of neural tube defects in humans after first-trimester exposure. Efavirenz can be used after the first trimester, if indicated, to avoid drug interactions between anti-TB drugs and PIs. Initiation of nevirapine is not recommended for women with CD4+ counts >250 cells/microliter because of an increased risk for potentially fatal liver toxicity. For women who require ART strictly for prophylaxis of perinatal HIV transmission, use of a triple nucleoside regimen, including abacavir, could be considered to avoid interactions with TB drugs.

Disseminated *Mycobacterium avium* Complex (MAC) Disease

Preventing Exposure

MAC organisms commonly contaminate environmental sources (e.g., food and water). Available information does not support specific recommendations regarding avoidance of exposure.

Preventing Disease

Initiating Primary Prophylaxis

HIV-infected adults and adolescents should receive chemoprophylaxis against disseminated MAC disease if they have a CD4+ count of <50 cells/microliters (**AI**). Azithromycin or clarithromycin are the preferred prophylactic agents (**AI**). The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used (**EI**). The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared with azithromycin alone do not warrant a routine recommendation for this regimen (**CI**). Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections (**BII**). If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for MAC disease, although

drug interactions might complicate the use of this agent (**BI**). Before prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment, which might include obtaining a blood culture for MAC. Because treatment with rifabutin could result in RIF resistance among persons who have active TB, active TB also should be excluded before rifabutin is used for prophylaxis.

Although detecting MAC organisms in the respiratory or gastrointestinal tract might predict disseminated MAC infection, no data are available regarding efficacy of prophylaxis with clarithromycin, azithromycin, rifabutin, or other drugs among asymptomatic patients harboring MAC organisms at these sites in the presence of a negative blood culture. Therefore, routine screening of respiratory or gastrointestinal specimens for MAC is not recommended (**DIII**).

Discontinuing Primary Prophylaxis

Primary MAC prophylaxis should be discontinued among adult and adolescent patients who have responded to ART with an increase in CD4+ counts to >100 cells/microliter for $\geq$3 months (**AI**).

Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/microliter (**AIII**).

Treatment of Disease

Initial treatment of MAC disease should consist of two antimycobacterial drugs to prevent or delay the emergence of resistance (**AI**). Clarithromycin is the preferred first agent (**AI**); it has been studied more extensively than azithromycin in patients with AIDS and appears to be associated with more rapid clearance of MAC from the blood. However, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin (**AII**). Testing MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients (**BIII**).

EMB is the recommended second drug (**AI**). Some clinicians would add rifabutin as a third drug (**CI**).

The addition of a third or fourth drug should be considered in persons with advanced immunosuppression ($CD4^+$ count <50 cells/microliter), high mycobacterial loads (>2 $\log_{10}$ colony forming units/mL of blood), or in the absence of effective ART, settings in which mortality is increased and emergence of drug resistance is most likely (**CIII**). On the basis of data in non-HIV-infected patients, the third or fourth drug might include an injectable agent such as amikacin or streptomycin (**CIII**).

Patients who have disseminated MAC disease and have not been treated previously with or are not receiving effective ART should typically have ART withheld until after the first 2 weeks of antimycobacterial therapy have been completed to reduce risk for drug interactions, pill burden, and complications associated with the occurrence of IRIS (**CIII**). If ART has already been instituted, it should be continued and optimized unless drug interactions preclude the safe concomitant use of antiretroviral and antimycobacterial drugs (**CIII**).

Monitoring and Adverse Events, Including IRIS

A repeat blood culture for MAC should be obtained 4 to 8 weeks after initiating antimycobacterial therapy only for patients who fail to have a clinical response to their initial treatment regimen. Improvement in fever and a decline in quantity of mycobacteria in blood or tissue can be expected within 2 to 4 weeks after initiation of appropriate therapy; however, for those with more extensive disease or advanced immunosuppression, clinical response might be delayed.

Adverse effects with clarithromycin and azithromycin include nausea, vomiting, abdominal pain, abnormal taste, and elevations of liver transaminase levels or hypersensitivity reactions. Doses of clarithromycin >1 g per day for treatment of disseminated MAC disease have been associated with increased mortality and should not be used (**EI**). Rifabutin doses of $\geq$450 mg/day have been associated with higher risk for adverse drug interactions when used with clarithromycin or other drugs that inhibit cytochrome p450 (CYP450) isoenzyme 3A4 and might be associated with a higher risk for experiencing uveitis or other adverse drug reactions.

Persons who develop moderate to severe symptoms typical of IRIS during ART, should receive initial treatment with nonsteroidal, anti-inflammatory agents (**CIII**). If IRIS symptoms do not improve, short-term (4 to 8 weeks) systemic corticosteroid therapy, in doses equivalent to 20 to 40 mg of oral prednisone daily, has been successful in reducing symptoms and morbidity (**CIII**).

Rifabutin should not be administered to patients receiving certain PIs and NNRTIs because the complex interactions have been incompletely studied and the clinical implications of those interactions are unclear. PIs can increase clarithromycin levels, but no recommendation to adjust the dose of either clarithromycin or PIs can be made on the basis of existing data. Efavirenz can induce metabolism of clarithromycin. This can result in reduced serum concentration of clarithromycin but increased concentration of the 14-OH active metabolite of clarithromycin. Although the clinical significance of this interaction is unknown, the efficacy of clarithromycin for MAC prophylaxis could be reduced because of this interaction. Azithromycin metabolism is not affected by the CYP450 system; azithromycin can be used safely in the presence of PIs or NNRTIs without concerns of drug interactions.

Management of Treatment Failure

Treatment failure is defined by the absence of a clinical response and the persistence of mycobacteremia after 4 to 8 weeks of treatment. Repeat testing of MAC isolates for susceptibility to clarithromycin and azithromycin is recommended for patients who relapse after an initial response. The majority of patients who experience failure of clarithromycin or azithromycin primary prophylaxis in clinical trials had isolates susceptible to these drugs at the time MAC disease was detected.

Because the number of drugs with demonstrated clinical activity against MAC is limited, results of susceptibility testing should be used to construct a new multi-drug regimen. The regimen should consist of at least two new drugs not used previously, to which the isolate is susceptible and selected from among the

following: EMB, rifabutin, amikacin, or a quinolone (moxifloxacin, ciprofloxacin, or levofloxacin), although data supporting a survival or microbiologic benefit when these agents are added have not been compelling (**CIII**). On the basis of data related to non-HIV-infected patients being treated for MAC, an injectable agent such as amikacin or streptomycin should be considered (**CIII**). Whether continuing clarithromycin or azithromycin despite resistance provides additional benefit is unknown (**CIII**). Clofazimine should not be used because randomized trials have demonstrated lack of efficacy and an association with increased mortality (**EII**). Other second-line agents (e.g., ethionamide, thiacetazone [not available in the US], or cycloserine) have been anecdotally combined with clarithromycin and azithromycin as salvage regimens. However, their role in this setting is not well defined. Among patients whose initial treatment for MAC disease has not been successful or who have antimycobacterial drug-resistant MAC disease, optimizing ART is an important adjunct to second-line or salvage therapy for MAC disease (**AIII**).

Adjunctive treatment of MAC disease with immunomodulators has not been thoroughly studied, and data are insufficient to support a recommendation for use (**DIII**).

Preventing Recurrence

Adult and adolescent patients with disseminated MAC disease should receive lifelong secondary prophylaxis (chronic maintenance therapy) (**AII**), unless immune reconstitution occurs as a result of ART.

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

Patients are at low risk for recurrence of MAC when they have completed a course of $\geq$12 months of treatment for MAC, remain asymptomatic with respect to MAC signs and symptoms, and have a sustained increase (e.g., >6 months) in their $CD4^+$ counts to >100 cells/microliter after ART. Although the numbers of patients who have been evaluated remain limited and recurrences could occur, based on the limited number of patients who have been evaluated and the inferences from more extensive data indicating the safety of discontinuing secondary prophylaxis for other OIs, discontinuing chronic maintenance therapy is reasonable (**BII**). Secondary prophylaxis should be reintroduced if the $CD4^+$ count decreases to <100 cells/microliter (**AIII**).

Special Considerations During Pregnancy

Chemoprophylaxis for MAC disease should be administered to pregnant women the same as for nonpregnant women and adolescents (**AIII**). Because of an increased risk for birth defects evident in certain animal studies, clarithromycin is not recommended as the first-line agent for prophylaxis or treatment of MAC in pregnancy (**DIII**). Two studies, each with slightly more than 100 women with first-trimester exposure to clarithromycin, did not demonstrate an increase in or specific pattern of defects, although an increased risk for spontaneous abortion was noted in one study. Azithromycin did not produce defects in animal studies, but experience for use in humans during the first trimester is limited. Azithromycin is recommended for primary prophylaxis in pregnancy (**BIII**). For

secondary prophylaxis (chronic maintenance therapy), azithromycin plus EMB are the preferred drugs (**BIII**).

Diagnostic considerations and indications for treatment of pregnant women are the same as among nonpregnant adults. On the basis of animal data discussed previously, azithromycin is preferred over clarithromycin as the second agent with EMB (**BIII**). Use of EMB should minimize concerns regarding drug interactions, allowing initiation of ART as soon as possible during pregnancy to decrease the risk for perinatal transmission of HIV. Pregnant women whose treatment failed on their primary regimen should be managed in consultation with infectious disease and obstetrical specialists.

Bacterial Respiratory Disease

Preventing Exposure

No effective means exist to reduce exposure to *Streptococcus (S.) pneumoniae* and *Haemophilus (H.) influenzae*, which are common in the community.

Preventing Disease

HIV-infected adults and adolescents who have a CD4+ count of >200 cells/microliter should be administered a single dose of 23-valent polysaccharide pneumococcal vaccine (PPV) unless they have received this vaccine during the previous 5 years (**AII**). The majority of HIV specialists believe that the potential benefit of pneumococcal vaccination in the U.S. outweighs the risk.

HIV-infected adults and adolescents who have a CD4+ count of <200 cells/microliter can be offered PPV (**CIII**). Clinical evidence has not confirmed efficacy in this group, but evidence documents the benefit for those who also start ART. Revaccination can be considered for persons who were initially vaccinated when their CD4+ counts were <200 cells/microliter and whose CD4+ counts have increased to >200 cells/microliter in response to ART (**CIII**).

The duration of the protective effect of primary pneumococcal vaccination is unknown; revaccination every 5 years may be considered (**CIII**). No evidence confirms clinical benefit from revaccination. Nevertheless, the recommendation to vaccinate is increasingly pertinent because of the increasing incidence of invasive infections with drug-resistant (including TMP-SMX-, macrolide-, and beta-lactam-resistant) strains of *S. pneumoniae*.

The incidence of *H. influenzae* type b (Hib) infection among HIV-infected adults is low. Therefore, Hib vaccine is not usually recommended for adult use (**DIII**).

Several factors are associated with a decreased risk for bacterial pneumonia, including the use of combination ART and TMP-SMX used for PCP prophylaxis. The use of antimicrobial prophylaxis to prevent bacterial pneumonia has been explored. In many studies, TMP-SMX, when administered daily for PCP prophylaxis, reduces the frequency of bacterial respiratory infections. This should be considered in selecting an agent for PCP prophylaxis (**AII**). However, indiscriminate use of this drug (when not indicated for PCP prophylaxis or other

specific reasons) might promote development of TMP-SMX-resistant organisms. Thus, TMP-SMX should not be prescribed solely to prevent bacterial respiratory infection (**DIII**). Similarly, clarithromycin administered daily or azithromycin administered weekly for MAC prophylaxis might be effective in preventing bacterial respiratory infections. This should be considered in selecting an agent for prophylaxis against MAC (**BII**). However, these drugs should not be prescribed solely for preventing bacterial respiratory infection (**DIII**).

An absolute neutrophil count that is depressed because of HIV disease or drug therapy is associated with an increased risk for bacterial infections, including pneumonia. To reduce the risk for such bacterial infections, health-care providers might consider taking steps to reverse neutropenia, either by stopping myelosuppressive drugs (**CII**) or by administering granulocyte-colony stimulating factor (G-CSF) (**CII**).

Modifiable factors associated with an increased risk for bacterial pneumonia include smoking cigarettes and other drugs, injection-drug use (IDU), and alcohol use. Clinicians should encourage cessation of these behaviors, although no data exist to indicate that cessation decreases risk (**CIII**).

Inactivated influenza vaccine should be administered annually to all HIV-infected persons during influenza season (**AIII**). This recommendation is pertinent to prevention of bacterial pneumonia, which might occur as a complication of influenza illness. Live attenuated influenza vaccine is contraindicated for HIV-infected persons (**EIII**).

Treatment of Disease

The principles of the treatment of community-acquired bacterial pneumonia are the same for HIV-infected persons as for HIV-uninfected persons. Usually, collection of specimens for microbiologic studies should be performed before the initiation of antibiotic therapy. However, antibiotic therapy should be administered promptly, without waiting for the results of diagnostic testing.

An assessment of disease severity and arterial oxygenation should be performed in all persons with pneumonia. Noninvasive measurement of arterial oxygen saturation via pulse oximetry is an appropriate screening test. However, arterial blood gas (ABG) analysis is indicated for persons with evidence of hypoxemia suggested by noninvasive assessment and for persons with tachypnea and/or respiratory distress. Criteria that were developed to assess community-acquired pneumonia (CAP) disease severity in HIV-uninfected persons have been found to be valid for HIV-infected persons. Unlike recommendations for CAP therapy in non-HIV patients, no HIV-infected patient should receive macrolide monotherapy because of the increased risk for drug-resistant *S. pneumoniae* in the HIV-infected patient.

Outpatient Treatment

HIV-infected persons who are being treated as outpatients should receive an oral beta-lactam plus an oral macrolide (**AII**). Preferred beta-lactams are high-dose amoxicillin and amoxicillin-clavulanate; cefpodoxime and cefuroxime are

alternatives. Preferred macrolides are azithromycin and clarithromycin. Oral doxycycline is an alternative to the macrolide (**CIII**).

For persons who are allergic to penicillin or who have received a beta-lactam within the previous 3 months, an oral respiratory fluoroquinolone (moxifloxacin, levofloxacin [750 mg/day], or gemifloxacin) should be used (**AII**). Respiratory fluoroquinolones are active against *M. tuberculosis*. Thus, persons with TB who are treated with fluoroquinolone monotherapy might respond initially, but this response might be misleading, might delay the diagnosis of TB and the initiation of appropriate multi-drug therapy, and might increase the risk for transmission of TB. Thus, fluoroquinolones should be used with caution in patients in whom TB is suspected but who are not being treated with concurrent standard four-drug TB therapy. Because HIV-infected persons have an increased incidence of TB and the presentation of TB can be varied in HIV-infected persons, fluoroquinolones should be used only when the presentation strongly suggests bacterial pneumonia.

Increasing pneumococcal resistance rates have suggested that empirical therapy with a macrolide alone cannot be routinely recommended (**DIII**). Patients who are receiving a macrolide for MAC prophylaxis should never receive macrolide monotherapy for empiric treatment of bacterial pneumonia.

Non-ICU Inpatient Treatment

HIV-infected persons who are being treated as inpatients should receive an intravenous (IV) beta-lactam plus a macrolide (**AII**). Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam. Doxycycline is an alternative to the macrolide (**CIII**).

For persons who are allergic to penicillin or who have received a beta-lactam within the previous 3 months, an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) should be used (**AII**). Because of the activity of fluoroquinolones against *M. tuberculosis* and the dangers of monotherapy in persons with TB, fluoroquinolones should be used with caution in patients in whom TB is suspected but is not being treated with concurrent standard four-drug TB therapy.

Increasing pneumococcal resistance rates have suggested that empirical therapy with a macrolide alone cannot be recommended routinely (**DIII**). Patients who are receiving a macrolide for MAC prophylaxis should never receive macrolide monotherapy for empiric treatment of bacterial pneumonia.

ICU Treatment

Persons with severe pneumonia who require intensive care should be treated with an IV beta-lactam plus either IV azithromycin (**AII**) or an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) (**AII**). Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam.

For persons who are allergic to penicillin or who have received a beta-lactam within the previous 3 months, aztreonam plus an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) should be used (**BIII**).

Infections with the overwhelming majority of CAP pathogens will be treated adequately by use of the recommended empirical regimens. The increased incidence of *P. aeruginosa* and *Staphylococcus aureus* as a cause of CAP is the exception. These pathogens occur in specific epidemiologic patterns with distinct clinical presentations, for which empirical antibiotic coverage might be warranted. Diagnostic tests (sputum Gram stain and culture) are likely to be of high yield for these pathogens, allowing early discontinuation of empirical treatment if results are negative.

Empiric Pseudomonas aeruginosa Treatment

If risk factors for *Pseudomonas* infection are present, an antipneumococcal, antipseudomonal beta-lactam plus either ciprofloxacin or levofloxacin (750 mg dose) should be used (**BIII**). Preferred beta-lactams are piperacillin-tazobactam, cefepime, imipenem, or meropenem. An antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin (**BIII**) or an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (**BIII**) are alternatives. For persons who are allergic to penicillin or who have received a beta-lactam within the previous 3 months, aztreonam can be used in place of the beta-lactam (**BIII**).

Empiric Staphylococcus aureus Treatment

If risk factors for *S. aureus* infection, including community-acquired methicillin-resistant *S. aureus*, are present, vancomycin (possibly in combination with clindamycin) or linezolid alone should be added to the antibiotic regimen (**BIII**).

Pathogen-Directed Therapy

When the etiology of pneumonia has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at that pathogen (**BIII**).

Switch from Intravenous to Oral Therapy

For patients with CAP who begin IV antibiotic therapy, switching to oral therapy should be considered when they are improving clinically, are able to swallow and tolerate oral medications, and have intact gastrointestinal function. Suggested criteria for clinical stability include oral temperature <37.8 degrees C, heart rate <100 beats/minute, respiratory rate <24 breaths/minute, systolic blood pressure $\geq$90 mm Hg, and room air oxygen saturation >90% or partial pressure of oxygen in arterial blood (PaO2) >60 mm Hg.

Monitoring and Adverse Events, Including IRIS

The clinical response to appropriate antimicrobial therapy is similar in HIV-infected and non-HIV-infected persons. A clinical response (i.e., a reduction in fever and improvement in respiratory symptoms, physical findings, and laboratory studies) are generally observed 48 to 72 hours after initiation of appropriate therapy. Usually, radiographic improvements might lag behind clinical improvement. If a patient has progressive pneumonia in spite of therapy, leading to severe CAP,

adjunctive therapy with corticosteroids might be appropriate to ameliorate the inflammatory reaction to killing bacteria in the lung parenchyma (**CIII**).

IRIS has not been described in association with bacterial respiratory disease and treatment with ART in HIV-infected persons.

Management of Treatment Failure

Persons who fail to respond to appropriate antimicrobial therapy should undergo further evaluation to search for other infectious and noninfectious causes of pulmonary dysfunction. The possibility of TB should always be considered in HIV-infected persons with pulmonary disease.

Preventing Recurrence

HIV-infected persons should receive pneumococcal and influenza vaccine as recommended. Clinicians can administer antibiotic chemoprophylaxis to HIV-infected patients who have frequent recurrences of serious bacterial respiratory infections (**CIII**). TMP-SMX, administered for PCP prophylaxis, and clarithromycin or azithromycin, administered for MAC prophylaxis, are appropriate for drug-sensitive organisms. However, health-care providers should be cautious when using antibiotics solely for preventing the recurrence of serious bacterial respiratory infections because of the potential development of drug-resistant microorganisms and drug toxicity.

Special Considerations During Pregnancy

The diagnosis of bacterial respiratory tract infections among pregnant women is the same as for nonpregnant adults, with appropriate shielding of the abdomen during radiographic procedures. Bacterial respiratory tracts infections should be managed as in the nonpregnant adult, with certain exceptions. Because of an increased risk for birth defects evident in some animal studies, clarithromycin is not recommended as the first-line agent among macrolides. Two studies, each involving at least 100 women with first-trimester exposure to clarithromycin, did not document a clear increase in or specific pattern of birth defects, although an increased risk for spontaneous abortion was noted in one study. Azithromycin did not produce birth defects in animal studies, but experience with human use in the first trimester is limited. Azithromycin is recommended when a macrolide is indicated in pregnancy (**BIII**). Arthropathy has been noted in immature animals exposed in utero to quinolones. However, approximately 400 cases of quinolone use in human pregnancies have been reported to various pregnancy registries, and use has not been associated with human arthropathy or birth defects after in utero exposure. Thus, quinolones can be used in pregnancy for serious respiratory infections when indicated (**CIII**). Doxycycline is not recommended for use during pregnancy because of increased hepatotoxicity and staining of fetal teeth and bones. Beta-lactam antibiotics have not been associated with teratogenicity or increased toxicity in pregnancy. Aminoglycosides may be used as needed. Although a theoretical risk for fetal renal or eighth nerve damage can occur with exposure during pregnancy, this finding has not been documented in humans except with streptomycin (10% risk) and kanamycin (2% risk). Experience with linezolid in human pregnancy has been limited, but it was not teratogenic in mice, rats, and rabbits.

Rates for preterm labor and preterm delivery are increased with pneumonia during pregnancy. Pregnant women with pneumonia after 20 weeks of gestation should be monitored for evidence of contractions (**BII**).

Pneumococcal vaccine can be administered during pregnancy (**AIII**). Although its safety during the first trimester of pregnancy has not been evaluated, no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. Inactivated influenza vaccine also can be administered during pregnancy, and influenza vaccine is recommended for all pregnant women who will be pregnant during influenza season (**AIII**). Live attenuated influenza vaccine should not be used during pregnancy (**EIII**). Because administration of vaccines might be associated with a transient rise in plasma HIV RNA levels, vaccination of pregnant women is recommended after ART has been initiated to minimize increases in plasma HIV RNA levels that might increase the risk for perinatal HIV transmission.

Bacterial Enteric Disease

Preventing Exposure

Scrupulous handwashing can reduce risk for diarrhea in HIV-infected persons, including diarrhea caused by enteric bacteria. HIV-infected persons should be advised to wash their hands after potential contact with human feces (e.g., defecation, cleaning feces from infants), after handling pets or other animals, after gardening or other contact with soil, before preparing food, before eating, and before and after sex (**AIII**). HIV-infected persons should avoid unprotected sex practices that might result in oral exposure to feces (e.g., anal sex, oral-anal contact) and in addition to hand-washing they should be advised to use barriers during sex to reduce exposures when possible (e.g., condoms, dental dams) (**AIII**).

Food

Health-care providers should advise HIV-infected persons, particularly those with a CD4+ count <200 cells/microliter, not to eat raw or undercooked eggs, including specific foods that might contain raw eggs (e.g., certain preparations of hollandaise sauce, Caesar and other salad dressings, certain mayonnaises (e.g., homemade), uncooked cookie and cake batter, and eggnog); raw or undercooked poultry, meat, and seafood (raw shellfish in particular); unpasteurized dairy products; unpasteurized fruit juices; and raw seed sprouts (e.g., alfalfa sprouts or mung bean sprouts) (**BIII**). Poultry and meat are safest when adequate cooking is confirmed by thermometer (i.e., internal temperature of 180 degrees F (82 degrees C) for poultry and 165 degrees F (74 degrees C) for red meats). If a thermometer is not used when cooking meats, the risk for illness is decreased by eating poultry and meat that have no trace of pink color. However, color change of the meat (e.g., absence of pink) does not always correlate with internal temperature. Produce should be washed thoroughly before being eaten (**BIII**).

Health-care providers should advise HIV-infected persons to avoid cross-contamination of foods. Uncooked meats, including hot dogs, and their juices should not come into contact with other foods (**BIII**). Hands, cutting boards,

counters, knives, and other utensils should be washed thoroughly after contact with uncooked foods (**BIII**).

Health-care providers should advise HIV-infected persons that, although the incidence of listeriosis is low, it is a serious disease that occurs with unusually high frequency among severely immunosuppressed HIV-infected persons. Immunosuppressed, HIV-infected persons who wish to reduce the risk for acquiring listeriosis should adhere to the following precautions (**CIII**):

- Avoid soft cheeses (e.g., feta, Brie, Camembert, blue-veined, and Mexican-style cheese such as queso fresco); hard cheeses, processed cheeses, cream cheese (including slices and spreads), cottage cheese, or yogurt need not be avoided.
- Cook leftover foods or ready-to-eat foods (e.g., hot dogs) until steaming hot before eating.
- Avoid foods from delicatessen counters (e.g., prepared salads, meats, cheeses) or heat/reheat these foods until steaming before eating.
- Avoid refrigerated pâtés and other meat spreads or heat/reheat these foods until steaming; canned or shelf-stable pâté and meat spreads need not be avoided.
- Avoid raw or unpasteurized milk (including goat's milk) or milk products or foods that contain unpasteurized milk or milk products.

Pets

HIV-infected persons should avoid direct contact with stool from new pets, dogs or cats aged <6 months, or stray pets (**BIII**). Gloves should always be worn when handling feces or cleaning areas that might have been contaminated by feces from pets (**BIII**). Persons should avoid or limit contact with reptiles (e.g., snakes, lizards, iguanas, and turtles) and chicks and ducklings because of the risk for salmonellosis (**BIII**).

Travel

The risk for foodborne and waterborne infections among immunosuppressed, HIV-infected persons is magnified during travel to economically developing countries. Persons who travel to such countries should avoid foods and beverages that might be contaminated, including raw fruits and vegetables, raw or undercooked seafood or meat, tap water, ice made with tap water, unpasteurized milk and dairy products, and items sold by street vendors (**AII**). Foods and beverages that are usually safe include steaming hot foods, fruits that are peeled by the traveler, bottled (including carbonated) beverages, hot coffee and tea, beer, wine, and water that is brought to a rolling boil for 1 minute. Treating water with iodine or chlorine might not be as effective as boiling and will not prevent infection with *Cryptosporidium* but can be used when boiling is not practical (**BIII**).

Preventing Disease

Prophylactic antimicrobial agents are not usually recommended for travelers (**DIII**). The effectiveness of these agents depends on gastrointestinal pathogens' local antimicrobial resistance patterns, which are seldom known. Moreover, these agents can elicit adverse reactions, promote the emergence of resistant

organisms, and increase risk for enteric *Clostridium difficile* infection. However, for HIV-infected travelers, antimicrobial prophylaxis can be considered, depending on the level of immunosuppression and the region and duration of travel (**CIII**). Use of fluoroquinolones or rifaximin can be considered when prophylaxis is deemed necessary (**CIII**). As an alternative (e.g., for pregnant women and persons already taking TMP-SMX for PCP prophylaxis), TMP-SMX might offer limited protection against traveler's diarrhea (**BIII**). Risk for toxicity should be considered before treatment with TMP-SMX is initiated solely because of travel.

Treatment of Disease

Immunocompetent hosts without HIV-1 infection often do not require treatment for *Salmonella* gastroenteritis; the condition is self-limited and treatment might prolong the carrier state. However, no treatment trials have examined this strategy of watchful waiting for spontaneous resolution among patients with HIV infection, and the risk for bacteremia is sufficiently high that most specialists recommend treatment of all HIV-associated *Salmonella* infections (**BIII**).

The initial treatment of choice for *Salmonella* infection is a fluoroquinolone (**AIII**). Ciprofloxacin is the preferred agent (**AIII**); other fluoroquinolones (levofloxacin and moxifloxacin) also would be effective in treatment of salmonellosis among HIV-infected persons, but these have not been well evaluated in clinical studies (**BIII**). Depending on antibiotic susceptibility, alternatives to the fluoroquinolones might include TMP-SMX or expanded spectrum cephalosporins (e.g., ceftriaxone or cefotaxime) (**BIII**).

The length of therapy for HIV-related *Salmonella* infection is poorly defined. For patients with CD4+ counts $\geq$200 cells/microliter and mild gastroenteritis, with or without bacteremia, 7 to 14 days of treatment for salmonellosis is reasonable (**BIII**); among patients with advanced HIV disease ($CD4^+$ <200 cells/microliter), a longer course of antibiotics (e.g., 2 to 6 weeks) is often recommended (**CIII**).

Therapy for shigellosis is indicated both to shorten the duration of illness and to prevent spread of the infection to others (**AIII**). The recommended treatment is with a fluoroquinolone for 3 to 7 days (**AIII**). Depending on antibiotic susceptibilities, alternatives to this treatment may include TMP-SMX for 3 to 7 days or azithromycin for 5 days (**BIII**). Cases of *shigellosis* acquired internationally have high rates of TMP-SMX resistance; in addition, HIV-infected persons have higher rates of adverse effects related to this agent. As a result, fluoroquinolones are preferred as first-line treatment. Treating patients who have *Shigella* bacteremia is less well defined. Depending on the severity of infection, extending treatment to 14 days is reasonable, using the agents described previously (**BIII**).

As with non-HIV-infected patients, the optimal treatment of campylobacteriosis among persons with HIV infection is poorly defined. Among patients with mild disease, some clinicians might opt to withhold therapy unless symptoms persist for more than several days. Increasing resistance to fluoroquinolones makes the choice of therapy especially problematic. For mild-to-moderate campylobacteriosis, initiating therapy with a fluoroquinolone (e.g., ciprofloxacin) or a macrolide (e.g., azithromycin), pending susceptibility test results, and treating for 7 days is a reasonable approach (**BIII**). Patients with bacteremia

should be treated for ≥2 weeks (**BIII**), and adding a second active agent (e.g., an aminoglycoside) might be prudent (**CIII**).

Monitoring and Adverse Events, Including IRIS

Patients should be monitored closely for response to treatment, as defined clinically by improvement in systemic signs and symptoms and resolution of diarrhea. A follow-up stool culture to demonstrate clearance of the organism is not generally required if a complete clinical response has been demonstrated, but should be considered for those patients who fail to respond clinically to appropriate antimicrobial therapy, or when public health considerations dictate the need to ensure microbiologic cure (e.g., health-care or food service workers). If after a diagnosis of gram-negative bacterial enteritis and diarrhea persists or recurs after intervention, other enteric infections should be considered, particularly *Clostridium difficile*.

IRIS has not been described in association with treatment for bacterial enteric diarrhea.

Management of Treatment Failure

Treatment failure is defined by the lack of improvement in clinical signs and symptoms of diarrheal illness and the persistence of organisms in stool, blood, or other relevant body fluids or tissue after completion of appropriate antimicrobial therapy for the recommended duration. Some patients with *Salmonella* bacteremia might remain febrile for 5 to 7 days despite effective therapy. Therefore, careful observation is required to determine the adequacy of the response.

Treatment should be guided by drug susceptibility testing of isolates recovered in culture. An evaluation of other factors that might contribute to failure or relapse, such as malabsorption of oral antibiotics, a sequestered focus of infection (e.g., an undrained abscess), adverse drug reactions that interfere with antimicrobial activity, or infection with other agents (e.g., *C. difficile*) should be undertaken as indicated.

Preventing Recurrence

HIV-infected persons who have *Salmonella* septicemia, which typically occurs in those with advanced HIV disease (e.g., CD4+ count <200 cells/microliter), should be monitored clinically for recurrence after treatment (**BIII**). For persons with recurrent *Salmonella* septicemia, 6 months or more of antibiotics treatment of acute disease should be considered as secondary prophylaxis, although the value of this intervention has not been established and must be weighed against the risks of long-term antibiotic exposure (**CIII**). In patients who have responded to ART, secondary prophylaxis can probably be stopped. Chronic suppressive or maintenance therapy is not recommended for *Campylobacter* or *Shigella* infections among persons with HIV infection (**EIII**). Household contacts of HIV-infected persons who have salmonellosis or shigellosis should be evaluated for persistent asymptomatic carriage of *Salmonella* or *Shigella* so that strict hygienic measures or antimicrobial therapy can be instituted and recurrent transmission to the HIV-infected person can be prevented (**BIII**).

Special Considerations During Pregnancy

The diagnosis of bacterial enteric infections among pregnant women is the same as among nonpregnant women. Bacterial enteric infections in the pregnant woman should be managed as in the nonpregnant woman, with several considerations. Arthropathy has been noted in immature animals when quinolones are used during pregnancy. However, approximately 400 cases of quinolone use in pregnancy have been reported to various pregnancy registries, and use has not been associated with arthropathy or birth defects after in utero exposure. Thus, quinolones can be used in pregnancy for bacterial enteric infections in HIV-infected pregnant women as indicated (**CIII**). Alternate agents for use in pregnancy include expanded spectrum cephalosporins, TMP-SMX, or azithromycin, depending on the organism and the results of susceptibility testing (**CIII**). Neonatal-care providers should be informed of maternal sulfa therapy if used near delivery because of the theoretical increased risk of hyperbilirubinemia and kernicterus to the newborn.

Bartonellosis

Preventing Exposure

HIV-infected persons, specifically those who are severely immunocompromised (CD4+ counts <100 cells/microliter), are at high risk for severe disease caused by *Bartonella (B.) quintana* and *B. henselae*. The major risk factors for acquisition of *B. henselae* are contact with cats infested with fleas and receiving cat scratches. Immunocompromised persons should consider the potential risks of cat ownership (**AIII**). Persons who acquire a cat should acquire an animal aged >1 year and in good health (**BII**). Cats should be acquired from a known environment, have a documented health history, and be free of fleas. Stray cats and cats with flea infestation should be avoided. Declawing is not advised, but HIV-infected persons should avoid rough play with cats and situations in which scratches are likely (**AII**). Patients should avoid contact with flea feces ("flea dirt"), and any cat-associated wound should be washed promptly (**BIII**). Care of cats should include a comprehensive, ongoing flea-control program under the supervision of a veterinarian (**BIII**). No evidence indicates any benefits to cats or their owners from routine culture or serologic testing of the pet for *Bartonella* infection or from antibiotic treatment of healthy, serologically positive cats (**DII**). The major risk factor for *B. quintana* infection is body lice infestation. Homeless or marginally housed persons should be informed that body louse infestation can be associated with serious illness and provided with appropriate measures to eradicate body lice, if present (**AII**).

Preventing Disease

Primary chemoprophylaxis for *Bartonella*-associated disease is not recommended (**DIII**). However, note that in a retrospective case-control study, MAC prophylaxis using a macrolide or rifamycin was protective against developing *Bartonella* infection.

Treatment of Disease

No randomized, controlled clinical trials have evaluated antimicrobial treatment of bartonellosis. Erythromycin and doxycycline have been used successfully to treat bacillary angiomatosis (BA), peliosis hepatica, bacteremia, and osteomyelitis and are considered first-line treatment for bartonellosis on the basis of reported experience in case series (**AII**). Therapy should be administered for ≥3 months (**AII**). Doxycycline, with or without RIF, is the treatment of choice for bartonellosis infection involving the CNS and other severe bartonellosis infections (**AIII**).

Clarithromycin or azithromycin treatment has been associated with clinical response and either of these can be an alternative for *Bartonella* treatment (**BIII**). Azithromycin is recommended for patients who are less likely to comply with the more frequent dosing schedule for doxycycline or erythromycin. Penicillins and first-generation cephalosporins have no in vivo activity and should not be used for treatment of bartonellosis (**DII**). Quinolones and TMP-SMX have variable in vitro activity and an inconsistent clinical response in case reports and are not recommended (**DIII**).

IRIS has not been described in association with *Bartonella* infection, but patients with *Bartonella* CNS or ophthalmic lesions should probably be treated with doxycycline and RIF for 2 to 4 weeks before instituting ART.

Monitoring and Adverse Effects, Including IRIS

Patients treated with oral doxycycline should be cautioned about pill-associated ulcerative esophagitis that occurs most often when a dose is taken with only a small amount of liquid or at night just before retiring (**AIII**).

No immune inflammatory response syndrome has been described in association with Bartonellosis and treatment with ART in HIV-infected persons.

Management of Treatment Failure

Among patients who fail to respond to initial treatment, one or more of the second-line alternative regimens should be considered (**AIII**).

Preventing Recurrence

Relapse can occur after a course of primary treatment. In this setting, long-term suppression of infection with doxycycline or a macrolide is recommended, as long as the CD4+ count remains <200 cells/microliter (**AIII**).

Long-term suppression can be discontinued after the patient has received 3 to 4 months of therapy and when the CD4+ count remains >200 cells/microliter for ≥6 months (**CIII**). Certain specialists would discontinue therapy only if the *Bartonella* titers have also decreased by fourfold (**CIII**).

Special Considerations During Pregnancy

Infection with *B. bacilliformis* in immunocompetent patients during pregnancy has been associated with increased complications and risk for death. No data are

available on the effect of *B. henselae* or *B. quintana* infections in pregnant women with concomitant HIV infection.

The approach to diagnosis of *Bartonella* infections in pregnant women is the same as in nonpregnant women. Erythromycin treatment should be used (**AIII**) rather than tetracyclines (**EII**) during pregnancy because of the increased risk for hepatotoxicity and the accumulation of tetracycline in fetal teeth and bones, resulting in dark, permanent staining of fetal teeth. Third-generation cephalosporins (e.g., ceftizoxime or ceftriaxone) might have efficacy against *Bartonella* in the pregnant HIV-infected woman, but should be considered second-line therapy after a macrolide. First- and second-generation cephalosporins are not recommended because of their lack of efficacy against *Bartonella* (**EII**).

Syphilis

Preventing Exposure

The resurgence of syphilis among persons with HIV infection in the U.S. underscores the importance of primary prevention of syphilis among persons with HIV infection. This should begin with routine discussion of sexual behaviors. Providers should discuss client-centered risk reduction messages and provide specific actions that can reduce the risk for acquiring sexually transmitted infections and for transmitting HIV. Routine serologic screening for syphilis is recommended at least annually for all sexually active HIV-infected persons, with more frequent screening (every 3 to 6 months) for those with multiple partners, unprotected intercourse, sex in conjunction with illicit drug use, methamphetamine use, or partners who participate in such activities. The occurrence of syphilis in an HIV-infected person is an indication of high-risk behavior and should prompt intensified counseling messages and strong consideration of referral for behavioral intervention. Persons undergoing screening or treatment for syphilis also should be evaluated for all common sexually transmitted diseases (STDs).

Preventing Disease

The same measures that apply to preventing exposure apply to preventing disease.

Treatment of Disease

Management of syphilis in HIV-infected patients is similar to the management in HIV-uninfected persons. However, closer follow-up is recommended to detect potential treatment failures or disease progression.

Penicillin remains the treatment of choice for syphilis regardless of HIV status. HIV-infected persons with early-stage (i.e., primary, secondary, or early-latent) syphilis should receive a single intramuscular (IM) injection of 2.4 million units of benzathine penicillin G (**AII**). Although most HIV-infected persons with early syphilis respond appropriately to standard benzathine penicillin, some specialists recommend two additional weekly benzathine penicillin injections. The benefit of this treatment approach remains unproven. Enhanced penicillin therapy (i.e.,

standard benzathine penicillin with high-dose oral amoxicillin and probenecid) did not improve clinical outcome in early-stage syphilis and is not recommended (**DII**).

The efficacy of alternative nonpenicillin regimens in HIV-infected persons with early syphilis, including oral doxycycline, ceftriaxone, and azithromycin, has not been evaluated sufficiently in HIV-infected persons to warrant use as first-line treatment. Regardless of HIV infection status, the use of any alternative penicillin treatment regimen should be undertaken only with close clinical and serologic monitoring (**BIII**). Similarly, although some evidence suggests that a single 2-gram oral dose of azithromycin might have efficacy for treating early syphilis, molecular resistance of *T. pallidum* to macrolides and clinical treatment failures with azithromycin have been reported; such treatment should be used only with close clinical and serologic monitoring to detect treatment failure (**CII**).

In HIV-infected persons with late-latent syphilis for whom the CSF examination excludes the diagnosis of neurosyphilis, treatment with three weekly IM injections of 2.4 million units benzathine penicillin G is recommended (**AIII**). Alternative therapy with doxycycline 100 mg by mouth twice a day for 28 days has not been sufficiently evaluated in HIV-infected persons to warrant use as first-line treatment (**BIII**). If the clinical situation requires the use of an alternative to penicillin, treatment should be undertaken with close clinical and serologic monitoring.

HIV-infected persons with clinical evidence of late-stage (tertiary) syphilis (cardiovascular or gummatous disease) should have a CSF examination to rule out neurosyphilis before initiating therapy. The complexity of tertiary syphilis management is beyond the scope of these guidelines and providers are advised to consult an infectious disease specialist.

HIV-infected persons with clinical or laboratory evidence of neurosyphilis (i.e., CNS, otic, or ocular disease) should receive IV aqueous crystalline penicillin G, 18 to 24 million units daily, administered 3 to 4 million units IV every 4 hours or by continuous infusion for 10 to 14 days (**AII**) or procaine penicillin 2.4 million units IM once daily plus probenecid 500 mg orally four times a day for 10 to 14 days (**BII**). HIV-infected persons who are allergic to sulfa-containing medications should not be administered probenecid because of potential allergic reaction (**DIII**).

Because neurosyphilis treatment regimens are of shorter duration than those used in late-latent syphilis, some specialists recommend 2.4 million units IM once per week for up to 3 weeks after completion of neurosyphilis treatment to provide a comparable duration of therapy (**CIII**). Among patients who are allergic to penicillin, penicillin desensitization is the preferred approach to treating neurosyphilis (**BIII**). However, limited data indicate that ceftriaxone (2 g daily IV for 10 to 14 days) might be an acceptable alternative regimen (**CIII**). Other alternative regimens for neurosyphilis have not been evaluated adequately.

Monitoring and Adverse Events, Including IRIS

Clinical and serologic responses to treatment of early stage (i.e., primary, secondary, and early-latent) disease should be monitored at 3, 6, 9, 12, and 24

months after therapy. Serologic responses to treatment are similar in persons with and without HIV infection; however, subtle variations might occur, including the temporal pattern of response.

After successful treatment for syphilis (HIV-infected and -uninfected persons), 15% to 20% of persons might remain "serofast," meaning that serum nontreponemal test titers remain reactive at low and unchanging titers, usually <1:8, for prolonged periods. This serofast state probably does not represent treatment failure. Serologic detection of potential reinfection should be based on at least a fourfold increase in titer above the established serofast baseline.

Response to therapy of late-latent syphilis should be monitored using nontreponemal serologic tests at 6, 12, 18, and 24 months to ensure at least a fourfold decline in titer. Some retrospective studies have documented concomitant HIV infection associated with poorer CSF and serologic responses to neurosyphilis therapy. CSF examination should be repeated at 6 months after completion of therapy. If clinical symptoms develop or nontreponemal titers rise fourfold, a repeat CSF examination should be performed and treatment administered accordingly. The earliest CSF indicator of response to neurosyphilis treatment is a decline in CSF lymphocytosis. The CSF VDRL might respond more slowly. Nontreponemal serum titers should be monitored during the next 12 to 24 months and if the titers do not decline fourfold, consultation with an infectious disease specialist is recommended.

No IRIS has been described in association with syphilis and treatment with ART in HIV-infected persons.

Management of Treatment Failure

Retreatment of patients with early-stage syphilis should be considered for those who 1) have a sustained fourfold increase in serum nontreponemal titers after an initial reduction after treatment, or 2) have persistent or recurring clinical signs or symptoms of disease (**BIII**). Certain specialists recommend retreating persons with early syphilis who do not experience at least a fourfold decrease in serum nontreponemal titers 6 to 12 months after therapy (**BIII**). If CSF examination does not confirm the diagnosis of neurosyphilis, such patients should receive 2.4 million units IM benzathine penicillin G administered at 1-week intervals for 3 weeks (**BIII**). Certain specialists also recommend a course of aqueous penicillin G administered IV or procaine penicillin administered IM plus probenecid for treatment of neurosyphilis in this setting although data to support this practice are lacking (**CIII**). If titers do not respond appropriately after retreatment, the value of repeated CSF examination or additional therapy has not been established. Persons with HIV infection might be at increased risk for treatment failure and neurologic complications; the magnitude of these risks is not precisely defined but is likely low.

Patients with late-latent syphilis should have a repeat CSF examination and be retreated if they have clinical signs or symptoms of syphilis, have a fourfold increase in serum nontreponemal test titer, or experience an inadequate serologic response (less than fourfold decline in nontreponemal test titer) within 12 to 24 months of therapy (**BIII**). If the CSF examination is consistent with CNS involvement, retreatment should follow the neurosyphilis recommendations

(**AIII**). Persons with latent syphilis and a normal CSF examination should be treated with benzathine penicillin, 2.4 million units IM weekly for 3 weeks (**BIII**); certain specialists recommend a neurosyphilis regimen in this setting (**CIII**). Retreatment for neurosyphilis should be considered if the CSF WBC count has not decreased after 6 months after completion of treatment or if the CSF-VDRL remains reactive 2 years after treatment (**BIII**).

Preventing Recurrence

No recommendations indicate the need for secondary prophylaxis or prolonged chronic maintenance antimicrobial therapy for syphilis in HIV-infected persons. Targeted mass treatment of high-risk populations has not been demonstrated to be effective and is not recommended. Azithromycin is not recommended as secondary prevention because of azithromycin treatment failures reported in HIV-infected persons and reports of macrolide-resistant *T. pallidum*.

Special Considerations During Pregnancy

Pregnant women should be screened for syphilis at the first prenatal visit. In areas where syphilis prevalence is high or among women at high risk (e.g., uninsured, women living in poverty, commercial sex workers, and IDUs), testing should be repeated at 28 to 32 weeks of gestation and at delivery. All women delivering a stillborn infant after 20 weeks of gestation should also be tested for syphilis. Syphilis screening also should be offered at sites providing episodic care to pregnant women at high risk, including emergency departments, jails, and prisons. No infant should leave the hospital without documentation of maternal syphilis serology status during pregnancy.

The rate of transmission to the fetus and adverse pregnancy outcomes of untreated syphilis are highest with primary, secondary, and early-latent syphilis during pregnancy and decrease with increasing duration of infection thereafter. Pregnancy does not appear to alter the course, manifestations, or diagnostic test results of syphilis infection among adults. Concurrent syphilis infection has been associated with increased risk for perinatal transmission of HIV to the infant.

Treatment during pregnancy should consist of the same penicillin regimen as recommended for the given disease stage among nonpregnant, HIV-infected adults. Because of treatment failures reported after single injections of benzathine penicillin G among HIV-uninfected pregnant women, certain specialists recommend a second injection 1 week after the initial injection for pregnant women with early syphilis. Because of additional concerns about the efficacy of standard therapy in HIV-infected persons, a second injection in 1 week for HIV-infected pregnant women should be considered (**BIII**).

No alternatives to penicillin have been proven effective and safe for treatment of syphilis during pregnancy or for prevention of fetal infection. Pregnant women who have a history of penicillin allergy should be referred for skin testing and desensitization and treatment with penicillin (**AIII**). Erythromycin does not reliably cure fetal infection; tetracyclines should not be used during pregnancy because of hepatotoxicity and staining of fetal bones and teeth (**EIII**). However, because of insufficient information regarding the use of azithromycin or ceftriaxone treatment in pregnancy, routine use is not recommended (**DIII**).

A Jarisch-Herxheimer reaction occurring during the second half of pregnancy might precipitate preterm labor or fetal distress. Women should be advised to seek obstetric attention after treatment if they notice contractions or a decrease in fetal movement during the first 24 hours after treatment. During the second half of pregnancy, syphilis management may be facilitated by a sonographic fetal evaluation for congenital syphilis, but this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis indicate a greater risk for fetal treatment failure. Such cases should be managed in consultation with obstetric specialists. Evidence is insufficient to recommend specific regimens for these situations. After >20 weeks of gestation, fetal and contraction monitoring for 24 hours after initiation of treatment for early syphilis should be considered when sonographic findings indicate fetal infection.

Repeat serologic titers should be performed in the third trimester and at delivery for women treated for syphilis during pregnancy. Data related to serologic response to syphilis in HIV-infected women are insufficient. Titers can be conducted monthly for women at high risk for reinfection. Clinical and antibody response should be appropriate for the stage of disease, although the majority of women will deliver before their serologic response can be definitively assessed. Maternal treatment is likely to be inadequate if delivery occurs within 30 days of therapy, if clinical signs of infection are present at delivery or if the maternal antibody titer is fourfold higher than the pretreatment titer.

Mucocutaneous Candidiasis

Preventing Exposure

Candida organisms are common commensals on mucosal surfaces in healthy persons. No measures are available to reduce exposure to these fungi.

Preventing Disease

Data from prospective controlled trials indicate that fluconazole can reduce the risk for mucosal (e.g., oropharyngeal, esophageal, and vaginal) candidiasis among patients with advanced HIV disease. However, routine primary prophylaxis is not recommended because mucosal disease is associated with very low attributable mortality, acute therapy is highly effective, prophylaxis can lead to disease caused by drug-resistant species, prophylactic agents can produce drug interactions, and prophylaxis is expensive (**DIII)**. ART does reduce the likelihood of mucosal candidiasis (**AI**).

Treatment of Disease

Oral fluconazole is as effective and, in certain studies, superior to topical therapy for oropharyngeal candidiasis. In addition, it is more convenient and typically better tolerated. Therefore, oral fluconazole is considered the drug of choice (**AI**).

Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or once-daily miconazole mucoadhesive tablets (**BII**).

Itraconazole oral solution for 7 to 14 days is as effective as oral fluconazole but less well tolerated (**AI**). Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole (**AI**). They are alternatives to oral fluconazole, although few situations require that these drugs would be used in preference to fluconazole solely to treat mucosal candidiasis. In a multicenter, randomized study, posaconazole was proven more effective than fluconazole in sustaining clinical success after antifungal therapy was discontinued. Ketoconazole and itraconazole capsules are less effective than fluconazole because of their more variable absorption. Using these agents to treat mucosal candidiasis is not reasonable if the other options are available (**DIII**).

Systemic antifungals are required for effective treatment of esophageal candidiasis (**AI**). A 14- to 21-day course of either fluconazole (oral or IV) or oral itraconazole solution is highly effective (**AI**). As with oropharyngeal candidiasis, oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption (**DII**). Although IV caspofungin (**BI**) or IV voriconazole (**BI**) are effective in treating esophageal candidiasis among HIV-infected patients, oral or IV fluconazole remain the preferred therapies **(AI)**.

Two additional parenteral echinocandins, micafungin and anidulafungin, also are approved for the treatment of esophageal candidiasis. Although the three echinocandins are as effective as fluconazole in the treatment of esophageal candidiasis, they all appear to have a greater relapse rate when compared with fluconazole. Although symptoms of esophageal candidiasis might be mimicked by other pathogens, a diagnostic trial of antifungal therapy is usually appropriate before endoscopy is used to identify causes of esophagitis (**CII**).

Vulvovaginal candidiasis in HIV-infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies including the following regimens:

- Oral fluconazole (**AII**)
- Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) (**AII**)
- Itraconazole oral solution (**BII**)

Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for $\geq$7 days (**AIII**).

ART reduces the frequency of mucosal candidiasis. Refractory cases of mucosal candidiasis typically resolve when immunity improves in response to ART.

IRIS has not been reported in association with episodes of mucosal candidiasis in HIV-positive persons.

Monitoring and Adverse Events, Including IRIS

For the majority of patients with mucocutaneous candidiasis, response to therapy is rapid, with improvement in signs and symptoms within 48 to 72 hours. Short courses of topical therapy rarely result in adverse effects, although patients might experience cutaneous hypersensitivity reactions, characterized rash, and pruritus.

Oral azole therapy can be associated with nausea, vomiting, diarrhea, abdominal pain, or transaminase elevations. If prolonged azole therapy is anticipated (>21 days), periodic monitoring of liver chemistry studies should be considered (**CIII**).

The echinocandins thus far appear to be safe and free of substantial side effects; histamine-related infusion toxicity, elevation of transaminase, and rash have been attributed to these drugs. No dose adjustments are required in renal failure.

IRIS has not been described because of *Candida*.

Management of Treatment Failure or Refractory Mucosal Candidiasis

Refractory oral or esophageal candidiasis is still reported in approximately 4% to 5% of HIV-infected persons, typically in those patients with CD4+ counts <50 cells/microliter who have received multiple courses of azole antifungals.

Treatment failure is typically defined as signs and symptoms of oropharyngeal or esophageal candidiasis that persist after more than 7 to 14 days of appropriate therapy. Oral itraconazole solution is effective at least transiently in approximately two thirds of persons with fluconazole-refractory mucosal candidiasis (**AII**). Posaconazole immediate-release oral suspension (400 mg twice daily [bid] for 28 days) is effective in 75% of patients with azole refractory oropharyngeal and/or esophageal candidiasis (**AII**).

IV amphotericin B is usually effective and can be used among patients with refractory disease (**BII**). Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used (**BII**).

Amphotericin B oral suspension (1 mL four times daily of the 100 mg/mL suspension) is sometimes effective among patients with oropharyngeal candidiasis who do not respond to itraconazole **(CIII)**. However, this product is not available in the U.S.

Azole-refractory esophageal candidiasis also can be treated with posaconazole (**AII**), anidulafungin (**BII**), caspofungin (**CII**), micafungin (**CII**), or voriconazole (**CIII**).

Preventing Recurrence

As with primary prophylaxis, the majority of HIV specialists do not recommend secondary prophylaxis (chronic maintenance therapy) for recurrent oropharyngeal or vulvovaginal candidiasis because of the effectiveness of therapy for acute disease, the low mortality associated with mucosal candidiasis, the potential for resistant *Candida* organisms to develop, the possibility of drug interactions, and the cost of prophylaxis (**DIII**). However, if recurrences are frequent or severe, oral fluconazole can be used for either oropharyngeal (**BI**) or vulvovaginal (**CI**) candidiasis. A recent randomized clinical trial has documented that the number of episodes of oropharyngeal candidiasis and other invasive fungal infections was statistically significantly lower in HIV patients with CD4+ count <150 cells/microliter when receiving continuous (three times a week) fluconazole versus episodic treatment of recurrences. This clinical trial also proved that the

development of clinically significant resistance was not higher in the group of continuous prophylaxis than in the group with episodic administration of fluconazole, provided that patients received ART.

The decision to use secondary prophylaxis should take into account the effect of recurrences on the patient's well-being and quality of life; the need for prophylaxis for other fungal infections; cost, toxicities, and most importantly, drug interactions.

For recurrent esophageal candidiasis, daily fluconazole can be used (**BI**). Oral posaconazole bid is also effective (**BII**). However, potential azole resistance should be considered when long-term azoles are considered.

Secondary prophylaxis should be instituted in those patients with fluconazole-refractory oropharyngeal or esophageal candidiasis who have responded to echinocandins, voriconazole, or posaconazole therapy because of high relapse rate until ART produces immune reconstitution (**CI**).

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

In situations where secondary prophylaxis is instituted, no data support a recommendation regarding discontinuation. On the basis of experience with other OIs, discontinuing secondary prophylaxis when the CD4+ count has risen to 200 cells/microliter because of ART would be reasonable (**CIII**).

Special Considerations During Pregnancy

Pregnancy increases the risk for vaginal colonization with *Candida* species. Diagnosis of oropharyngeal, esophageal, and vulvovaginal candidiasis is the same as among nonpregnant women.

Topical therapy is preferred for treatment of oral or vaginal candidiasis in pregnancy when possible (**BIII**). Single-dose, episodic treatment with fluconazole has not been associated with birth defects in humans. However, with chronic use of doses of fluconazole of 400 mg or higher in pregnancy, five cases of a syndrome of craniosynostosis, characteristic facies, digital synostosis, and limb contractures have been reported ("fluconazole embryopathy"). On the basis of these data, substitution of amphotericin B for high-dose fluconazole in the first trimester is recommended for invasive or refractory esophageal candidal infections (**AIII**). Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia. Itraconazole has been teratogenic in animals at high doses, but the metabolic mechanism accounting for these defects is not present in humans, so data are not applicable. Case series in humans do not suggest an increased risk for birth defects with itraconazole, but experience is limited. Posaconazole was associated with skeletal abnormalities in rats at doses similar to human levels and was embryotoxic in rabbits. No human data are available for posaconazole. Voriconazole is FDA category D because of cleft palate and renal defects seen in rats and embryotoxicity in rabbits. No human data on use of voriconazole are available, so use in the first trimester is not recommended. Multiple anomalies are seen in animals with micafungin; ossification defects have been seen with anidulafungin and caspofungin. No

human data are available for these drugs, and their use in human pregnancy is not recommended (**DIII**).

Chemoprophylaxis, either primary or secondary, against oropharyngeal, esophageal, or vaginal candidiasis using systemically absorbed azoles should not be initiated during pregnancy (**DIII**), and prophylactic azoles should be discontinued for HIV-infected women who become pregnant (**AIII**).

Cryptococcosis

Preventing Exposure

HIV-infected persons cannot completely avoid exposure to *Cryptococcus neoformans*. Limited epidemiologic evidence suggests that specific activities, including exposure to bird droppings, lead to an increased risk for infection.

Preventing Disease

Because the incidence of cryptococcal disease is low, routine testing of asymptomatic persons for serum cryptococcal antigen is not recommended (**DIII**).

Prospective, controlled trials indicate that fluconazole and itraconazole can reduce the frequency of primary cryptococcal disease among patients who have CD4+ counts <50 cells/microliter. However, the majority of HIV specialists recommend that antifungal prophylaxis not be used routinely to prevent cryptococcosis because of the relative infrequency of cryptococcal disease, lack of survival benefits associated with prophylaxis, possibility of drug interactions, potential antifungal drug resistance, and cost (**DIII**). The need for primary prophylaxis or suppressive therapy for other fungal infections (e.g., candidiasis, histoplasmosis, or coccidioidomycosis) should be considered when making decisions concerning primary prophylaxis for cryptococcosis.

Treatment of Disease

The recommended initial standard treatment is amphotericin B deoxycholate, at a dose of 0.7 mg/kg daily, combined with flucytosine, at a dose of 100 mg/kg daily in four divided doses, for $\geq$2 weeks for those with normal renal function (**AI**). Renal function should be monitored closely and the flucytosine dose adjusted appropriately for patients with renal impairment. The addition of flucytosine to amphotericin B during acute treatment is associated with more rapid sterilization of CSF. The combination of amphotericin B deoxycholate with fluconazole, 400 mg daily (**BII**), is inferior to amphotericin B combined with flucytosine for clearing *Cryptococcus* from CSF but is more effective than amphotericin B alone (**BII**).

On the basis of data from published and unpublished studies, a dose of 4 to 6 mg/kg daily for lipid formulations of amphotericin B is recommended (**AII**).

Fluconazole (400 to 800 mg daily) combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is inferior to amphotericin B and is

recommended only for persons who are unable to tolerate or unresponsive to standard treatment (**CII**).

After at least a 2-week period of successful induction therapy, defined as substantial clinical improvement and a negative CSF culture after repeat lumbar puncture, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole 400 mg daily (**AI**). This therapy should continue for 8 weeks (**AI**). Itraconazole is an acceptable though less effective alternative (**BI**). Limited data are available for the newer triazoles, voriconazole and posaconazole, as either primary or follow-up therapy for patients with cryptococcosis. Voriconazole should be used cautiously with HIV PIs and efavirenz.

Monitoring and Adverse Events, Including IRIS

Increased ICP can cause clinical deterioration despite a microbiologic response and is more likely if the CSF opening pressure is >20 cm H_2O. In one large clinical trial, 93% of deaths that occurred within the first 2 weeks of therapy and 40% of deaths that occurred within weeks 3 to 10 were associated with increased ICP.

At time of diagnosis, all patients with cryptococcal meningitis should have their opening pressure measured in the lateral decubitus position with good manometrics assured; normal values are <25 cm H_20. Patients with confusion, blurred vision, papilledema, lower extremity clonus, or other neurologic signs of increased ICP should be managed using measures to decrease ICP. Daily lumbar punctures are usually recommended for initial management. One approach is to remove a volume (typically 20–30 mL) of CSF that halves the opening pressure. CSF shunting should be considered for patients in whom daily lumbar punctures are no longer tolerated or whose signs and symptoms of cerebral edema are not being relieved (**BIII**). Corticosteroids, mannitol, and acetazolamide are not recommended (**DIII**).

After the initial 2 weeks of treatment, a repeat lumbar puncture should be performed to ensure the organism has been cleared from the CSF, even among those who have improved after the initial 2 weeks of treatment. Positive CSF cultures after 2 weeks of therapy are predictive of future relapse and typically less favorable clinical outcomes. If new symptoms or clinical findings occur later, a repeat lumbar puncture, with measurement of opening pressure and CSF culture, should be performed.

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Preinfusion administration of 500 mL of normal saline appears to reduce the risk for nephrotoxicity during treatment. Infusion-related adverse reactions may be ameliorated by pretreatment with acetaminophen and diphenhydramine; in rare cases, glucocorticosteroids administered approximately 30 minutes before the infusion might be required (**CIII**).

Patients receiving flucytosine should have flucytosine blood levels monitored to prevent bone marrow suppression and gastrointestinal toxicity; peak serum levels, which occur 2 hours after an oral dose, should not exceed 75 micrograms/mL. Persons treated with fluconazole should be monitored for hepatotoxicity.

An estimated 30% of patients with cryptococcal meningitis and HIV infection experience IRIS after initiation or reinitiation of ART. Patients who have cryptococcal IRIS are more likely to be antiretroviral naïve and have higher HIV RNA levels. Appropriate management of IRIS is to continue ART and antifungal therapy (**AII**). In patients with severely symptomatic IRIS, short-course glucocorticosteroids are recommended by certain specialists (**BIII**). Delaying the initiation of potent ART might be prudent, at least until the completion of induction therapy (the first 2 weeks) for severe cryptococcosis, especially if patients have elevated ICP (**CIII**).

Management of Treatment Failure

Treatment failure is defined as either the lack of clinical improvement after 2 weeks of appropriate therapy, including management of increased ICP, or relapse after an initial clinical response, defined as either a positive CSF culture and/or a rising CSF cryptococcal antigen titer with an associated compatible clinical picture. Although fluconazole resistance has been reported with *C. neoformans*, it is rare in the U.S. At this time, susceptibility testing is not recommended routinely (**DII**).

The optimal therapy for patients with treatment failure has not been established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs (**BIII**). Liposomal amphotericin B (4 to 6 mg/kg/day) might have improved efficacy over the deoxycholate formulation and should be considered in treatment failures (**AII**). Higher doses of fluconazole in combination with flucytosine also might be useful (**BIII**). Caspofungin and other echinocandins have no in vitro activity against *Cryptococcus species (spp.)* and no role in the clinical management of these patients. The newer triazoles, posaconazole and voriconazole, have activity against *Cryptococcus spp*. in vitro and might have a role in therapy.

Preventing Recurrence

Patients who have completed the initial 10 weeks of therapy for acute cryptococcosis should be administered chronic maintenance therapy with fluconazole 200 mg daily, either lifelong or until immune reconstitution occurs as a consequence of ART (**AI**). Itraconazole is inferior to fluconazole for preventing relapse of cryptococcal disease (**BI**).

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

The risk for recurrence of cryptococcosis appears low when patients have successfully completed a course of initial therapy, remain asymptomatic with regard to signs and symptoms of cryptococcosis, and have a sustained increase (i.e., >6 months) in their CD4+ counts to $\geq$200 cells/microliter after ART. On the basis of two published studies and inference from data regarding safety of discontinuing secondary prophylaxis for other OIs during advanced HIV disease, discontinuing chronic maintenance therapy among such patients who have successfully completed a course of initial therapy when the CD4+ count is consistently >200 cells/microliter is reasonable (**BII**) Certain HIV specialists would perform a lumbar puncture to determine if the CSF is culture negative and antigen negative before stopping therapy even if patients are asymptomatic

(**CIII**). Maintenance therapy should be reinitiated if the $CD4^+$ count decreases to <200 cells/microliter (**AIII**).

Special Considerations During Pregnancy

The diagnosis and treatment of cryptococcal infections during pregnancy is similar to that in nonpregnant adults with the following considerations regarding the use of antifungal during pregnancy. Because of their risk for teratogenicity, azole antifungals should be avoided during the first trimester of pregnancy (**EII**). Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Histoplasmosis

Preventing Exposure

Although HIV-infected persons living in or visiting areas in which histoplasmosis is endemic cannot completely avoid exposure, those whose CD4+ counts are $\leq$150 cells/microliter should avoid activities known to be associated with increased risk **(CIII)**. Such activities include creating dust when working with surface soil; cleaning chicken coops that are contaminated with droppings; disturbing areas contaminated with bird or bat droppings; cleaning, remodeling, or demolishing old buildings; and exploring caves (**CIII**).

Preventing Disease

Initiating Primary Prophylaxis

Prophylaxis with itraconazole at a dose of 200 mg daily can be considered for patients with CD4+ counts $\leq$150 cells/microliter who are at high risk because of occupational exposure or who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) (**CI**).

Discontinuing Primary Prophylaxis

If used, primary prophylaxis can be discontinued once peripheral blood CD4+ counts are >150 cells/microliter for 6 months in patients on potent ART (**BIII**). Prophylaxis should be restarted if the CD4+ counts fall to $\leq$150 cells/microliter (**CIII**).

Treatment of Disease

Patients with moderately severe to severe disseminated histoplasmosis should be treated with an IV lipid formulation of amphotericin B for $\geq$2 weeks (or until they improve clinically) followed by oral itraconazole (200 mg three times daily for 3 days and then 200 mg twice daily for a total of >12 months) (**AI**).

In a randomized clinical trial, liposomal amphotericin B at 3.0 mg/kg daily was more effective than standard amphotericin B deoxycholate at 0.7 mg/kg daily, inducing a more rapid and more complete response, lowering mortality, and

reducing toxicity. Substitution with amphotericin B lipid complex (ABLC) at 5.0 mg/kg daily may be an alternative because of cost or tolerability (**CIII**).

In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for 3 days followed by 200 mg twice daily is appropriate initial therapy (**AII**). The liquid formulation of itraconazole is preferred, owing to better absorption and fewer food interactions.

For persons with confirmed meningitis, liposomal amphotericin B should be administered as initial therapy for 4 to 6 weeks at a dosage of 5 mg/kg daily. This should be followed by maintenance therapy with itraconazole at a dose of 200 mg two or three times daily for a total of $\geq$1 year and until resolution of abnormal CSF findings (**AII**).

Posaconazole has been reported in some salvage studies to be of some benefit. Fluconazole has limited to no activity against histoplasmosis and should not be used. The role of other azoles, including voriconazole, is not clear. Voriconazole should be used cautiously with HIV PIs and efavirenz. No published data exist regarding the use of echinocandins for treating patients with histoplasmosis.

Acute pulmonary histoplasmosis in an HIV-infected patient with intact immunity, as indicated by a CD4+ count >300 cells/microliter, should be managed in a manner similar to that used for a nonimmunocompromised host (**AIII**).

Monitoring and Adverse Events, Including IRIS

Serial monitoring of serum or urine for *Histoplasma* antigen is useful for determining response to therapy. A rise in level is suggestive of a relapse (**AIII**). Because absorption of itraconazole can be erratic, serum itraconazole levels should be obtained at least once in all patients to ensure adequate absorption (**AIII**). The serum concentration should be >1 microgram/mL, ideally drawn for reasons of consistency as a trough level after at least 7 days on the current regimen. Itraconazole solution is recommended over the capsule formulation because absorption is improved, but this has not been studied specifically in AIDS patients.

IRIS has been reported uncommonly in patients with histoplasmosis. ART should not be withheld because of concern for the possible development of IRIS (**AIII**).

Management of Treatment Failure

Posaconazole solution at 800 mg daily was recently reported to be successful in three patients with HIV infection whose other previous therapies had failed. Voriconazole has been used in several transplant recipients and in one patient with AIDS who failed or could not tolerate therapy with other agents. Cross resistance between fluconazole and voriconazole has been noted in vitro.

Preventing Recurrence

Long-term suppressive therapy with itraconazole (200 mg daily) should be administered for patients with severe disseminated or CNS infection (**AII**) and in

patients who relapse despite receipt of appropriate therapy (**CIII**). Fluconazole 800 mg daily is less effective than itraconazole (**CII**). The role of voriconazole and posaconazole is not clear, but both have been used successfully in patients with histoplasmosis.

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

An AIDS Clinical Trials Group (ACTG)-sponsored study reported that discontinuing itraconazole was safe for patients who have been treated for histoplasmosis and who have a good immunologic response to ART. In that trial, patients had received $\geq$1 year of itraconazole therapy, had negative blood cultures, *Histoplasma* serum antigen <2 units, CD4+ counts >150 cells/microliter, and had been on ART for 6 months. No relapses were evident in 32 subjects who were followed for a median of 24 months. Thus, discontinuing suppressive azole therapy appears to be safe for patients who meet the criteria described above (**AI**). Suppressive therapy should be resumed if the CD4+ count decreases to <150 cells/microliter (**BIII**).

Special Considerations During Pregnancy

Because of their risk for teratogenicity, azoles should not be used during the first trimester of pregnancy (**EII**). Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Coccidioidomycosis

Preventing Exposure

Although HIV-infected persons cannot completely avoid activities involving extensive exposure to infection while living in or visiting areas in which *Coccidioides spp*. is endemic, they should avoid activities involving extensive exposure to disturbed native soil, such as occurs at building excavation sites or during dust storms (**CIII**).

Preventing Disease

Initiating Primary Prophylaxis

Within an area where the disease is endemic, a positive immunoglobulin M (IgM) or IgG serologic test indicates an increased risk for the development of active infection and specialists would recommend treatment if the CD4+ count is <250 cells/microliter (**BIII**). Yearly testing for seronegative HIV-infected persons living in such regions is reasonable (**CIII**).

Although highly immunosuppressed patients might benefit from primary prophylaxis, such therapy for HIV-infected persons without a positive IgM or IgG serologic test who live in the area where disease is endemic is not recommended (**DIII**). However, several clinicians would empirically provide chemoprophylaxis with either oral fluconazole 400 mg daily or itraconazole 200 mg bid if there were a positive IgM or IgG serologic test and the CD4 cell count was <250

cells/microliter (**CIII**). Outside the region in which coccidioidomycosis is endemic, routine testing does not appear to be useful and should not be performed (**DIII**).

Discontinuing Primary Prophylaxis

If used, primary prophylaxis can be discontinued once peripheral blood CD4+ counts are $\geq$250 cells/microliter for 6 months (**CIII**). Primary prophylaxis should be restarted if the CD4+ count is <250 cells/microliter (**BIII**).

Treatment of Disease

For patients with clinically mild infection, such as focal pneumonia, or who have a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate (**BII**). Fluconazole or itraconazole at doses of 400 mg daily is recommended. Data are limited with regard to the newer triazoles, posaconazole and voriconazole, but these agents might be useful in cases that fail to respond to fluconazole or itraconazole. Voriconazole should be used cautiously with HIV PIs and efavirenz.

For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy (**AII**). Most experience has been with the deoxycholate formulation using 0.7 to 1.0 mg/kg daily as an initial dose. Data regarding lipid formulations of amphotericin B are limited, but these formulations are likely as effective.

Therapy with amphotericin B should continue until clinical improvement is observed. Certain specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped (**BIII**).

Treatment of patients with coccidioidal meningitis requires consultation with a specialist. Therapy should begin with a triazole antifungal. Fluconazole at a dose of 400 to 800 mg daily is preferred (**AII**), but itraconazole has also been used successfully. Successful therapy with voriconazole and posaconazole has been described in case reports. Despite successful antifungal therapy, patients might develop hydrocephalus and require CSF shunting. In some instances, triazole antifungals are not effective. In such cases, intrathecal amphotericin B is recommended (**AIII**).

Monitoring and Adverse Events, Including IRIS

Monitoring the titer of the complement-fixing (CF) antibody is useful in assessing clinical response to therapy. This should be obtained every 12 weeks (**AIII**). A rise suggests recurrence of clinical disease. IRIS has not been observed in coccidioidomycosis.

Management of Treatment Failure

Patients whose therapy with fluconazole or itraconazole fails might be candidates for newer triazoles, but data regarding both posaconazole and voriconazole are limited. In most such instances, IV amphotericin B, in combination with triazole therapy, is recommended.

Preventing Recurrence

Patients who complete initial therapy for coccidioidomycosis should be considered for lifelong suppressive therapy using either fluconazole 400 mg daily or itraconazole 200 mg twice daily (**AII**).

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

Patients with focal coccidioidal pneumonia who have clinically responded to antifungal therapy appear to be at low risk for recurrence of coccidioidomycosis if their CD4+ counts are >250 cells/microliter and they are receiving ART. A reasonable plan for treating such patients is to discontinue secondary prophylaxis after 12 months of therapy (**CIII**) with continued monitoring for recurrence using serial chest radiographs and coccidioidal serology.

In patients with diffuse pulmonary disease or nonmeningeal disseminated coccidioidomycosis, relapses occur even in patients without HIV infection in 25% to 33% of cases. Even in patients with CD4+ counts >250 cells/microliter on potent ART, therapy should be continued indefinitely (**AIII**). For patients with meningitis, relapses have occurred in 80% of patients in whom triazoles have been discontinued. On the basis of this evidence, therapy for coccidioidal meningitis should be lifelong (**AII**).

Special Considerations During Pregnancy

Coccidioidomycosis is more likely to disseminate if acquired during the second or third trimester of pregnancy. Because of their risk for teratogenicity, azoles should not be used during the first trimester of pregnancy (**EII**). Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia. One problematic area is coccidioidal meningitis, in which the only alternative treatment is intrathecal amphotericin B. For such situations, the decision regarding choice of treatment should be made in consultation with the mother, infectious diseases consultant, and obstetrician.

Aspergillosis

Preventing Exposure

Aspergillus spp. are ubiquitous in the environment, and exposure is unavoidable. Avoiding particularly dusty environments is prudent, especially in areas such as those created by construction because spore counts might be higher in such settings.

Preventing Disease

No data on the prevention of primary aspergillosis in HIV-infected patients exists, although posaconazole has been reported to be effective among patients with hematologic malignancy and neutropenia.

Treatment of Disease

Treatment of aspergillosis in the HIV-infected population has not been examined systematically. The recommended treatment for invasive aspergillosis in patients without HIV infection is voriconazole. Voriconazole is the drug of choice but should be used cautiously with HIV PIs and efavirenz (**BIII**). Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives (**AIII**), as is caspofungin at 50 mg daily (**BII**) and posaconazole (**BII**). Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. Posaconazole also has proven to be useful in patients with invasive aspergillosis without HIV infection but is not approved for treatment of aspergillosis. The length of therapy is not established but should continue at least until the peripheral blood CD4+ count is >200 cells/microliter and there is evidence of clinical response.

Monitoring and Adverse Events, Including IRIS

IRIS has rarely been reported to occur in patients with invasive aspergillosis.

Management of Treatment Failure

The overall prognosis is poor among patients with advanced immunosuppression and in the absence of effective ART. No data are available to guide recommendations for the management of treatment failure. If voriconazole was used initially, substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be a reasonable choice for those who began therapy with voriconazole or posaconazole (**BIII**).

Preventing Recurrence

No data are available to base a recommendation for or against chronic maintenance or suppressive therapy among those who have successfully completed an initial course of treatment (**CIII**).

Special Considerations During Pregnancy

Because of their risk for teratogenicity, azoles should not be used during the first trimester of pregnancy (**EII**). (See "Mucocutaneous Candidiasis" above). Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Cytomegalovirus Disease

Preventing Exposure

HIV-infected persons who belong to groups at risk with relatively low seroprevalence rates for CMV and who, therefore, cannot be presumed to be seropositive should be tested for antibody to CMV (**BIII**). These groups include patients who have not had contact with men who have sex with men (MSM) or used injection drugs. HIV-infected adolescents and adults should be advised that CMV is shed in semen, cervical secretions, and saliva and that latex condoms must always be used during sexual contact to reduce the risk for exposure to CMV and to other sexually transmitted pathogens (**AII**).

HIV-infected adults and adolescents who provide child care or parents of children in day care facilities should be informed that they are at increased risk for acquiring CMV infection (**BI**). Similarly, parents and other caretakers of HIV-infected children should be advised of the increased risk to children at these centers (**BIII**). Risk for acquiring CMV infection can be diminished by optimal hygienic practices (e.g., hand-washing and use of latex gloves) (**AII**).

HIV-exposed infants and infected children, adolescents, and adults who are seronegative for CMV and who require blood transfusion should be administered only CMV antibody-negative or leukocyte-reduced cellular blood products in nonemergency situations (**BIII**).

Preventing Disease

CMV end-organ disease is best prevented using ART to maintain the CD4+ count >100 cells/microliter. Although oral valganciclovir would likely prevent the occurrence of CMV retinitis in patients with CD4+ counts <50 cells/microliter, such therapy is not usually recommended because of cost, the potential to induce CMV resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage (**DI**). The primary method for preventing severe CMV disease is recognizing the early manifestations of the disease. Patients should be made aware of the importance of increased floaters in the eye and should be advised to assess their visual acuity regularly by using simple techniques (e.g., reading newsprint) (**BIII**). Regular funduscopic examinations performed by an ophthalmologist are recommended by certain specialists for patients with low (e.g., <50 cells/microliter) CD4+ counts (**CIII**).

Observations suggest that pre-emptive anti-CMV treatment administered to patients who have evidence of active infection but who have not yet exhibited end-organ disease could be a therapeutic strategy for preventing CMV end-organ disease. Unless future studies document that clinical benefit can be obtained from pre-emptive therapy, the treatment of patients with CMV viremia in the absence of organ system involvement is not recommended (**DII**).

Treatment of Disease

Oral valganciclovir, IV ganciclovir, IV ganciclovir followed by oral valganciclovir, IV foscarnet, IV cidofovir, and the ganciclovir intraocular implant coupled with valganciclovir are all effective treatments for CMV retinitis (**AI**). Systemic therapy has been documented to reduce morbidity in the contralateral eye. This therapy should be considered when choosing among oral, IV, and local options. The choice of initial therapy for CMV retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment (**AIII**). No one regimen has been proven in a clinical trial to have superior efficacy related to protecting vision, and thus clinical judgment must be used when choosing a regimen.

The ganciclovir intraocular implant plus oral valganciclovir is superior to once daily intravenous ganciclovir (and presumably to once-daily oral valganciclovir) for preventing relapse of retinitis (**AI**). For this reason, certain HIV specialists recommend the intraocular implant plus valganciclovir as the preferred initial

therapy for patients with immediate sight- threatening lesions (adjacent to the optic nerve or fovea); for patients with small peripheral lesions oral valganciclovir alone may be adequate (**BII**). Certain ophthalmologists recommend an initial intravitreous injection of ganciclovir at the time CMV retinitis is diagnosed to deliver a high local concentration of ganciclovir to the eye immediately, until the ganciclovir implant can be placed (**CIII**).

Because ART can control CMV retinitis without anti-CMV therapy in patients who experience immune recovery, some clinicians might consider not treating small peripheral CMV lesions with anti-CMV therapy in ART-naïve patients. However, complications of CMV retinitis, including immune recovery retinitis and retinal detachment, are more common in patients with larger CMV lesions, and ART might take 3 to 6 months to fully control HIV replication and stimulate sufficient immune recovery to control the retinitis. Furthermore, consistent with natural history studies that associated CMV viremia with increased mortality in the pre- and current ART era, evidence indicates that anti-CMV therapy decreases mortality among patients with CMV retinitis and immune compromise. Therefore, even in ART-naïve patients with small peripheral lesions, treatment with systemic anti-CMV therapy, such as valganciclovir for the initial 3 to 6 months until ART has induced immune recovery, will likely be beneficial (**BII**).

For patients who have colitis or esophagitis, a majority of HIV specialists would recommend IV ganciclovir or foscarnet (or with oral valganciclovir if symptoms are not severe enough to interfere with oral absorption) for 21 to 28 days or until signs and symptoms have resolved (**BII**). Certain HIV specialists also would withhold therapy unless moderate-to-severe symptoms justify the use of systemic treatment if ART is to be initiated soon or can be optimized (**BIII**).

Criteria for establishing that CMV is the cause of pneumonitis and pulmonary dysfunction have been difficult to establish. If CMV is considered the cause of pulmonary dysfunction based on histology or cytology, treatment with IV ganciclovir, foscarnet, or cidofovir is logical, although few data establish that such therapy affects outcome (**CIII**).

For neurological disease, initiating therapy promptly is critical for an optimal clinical response. Although combination treatment with ganciclovir and foscarnet might be preferred as initial therapy to stabilize disease and maximize response (**BII**), this approach is associated with substantial rates of adverse effects, and optimal treatment for neurologic disease if ART can be optimized has not been established.

No data are available to demonstrate that starting ART among treatment-naïve patients with CMV retinitis would have an adverse effect on retinitis, gastrointestinal disease, or pneumonitis. Therefore, initiation of appropriate ART should be administered to those with acute CMV retinitis, gastrointestinal disease, or pneumonitis (**BIII**). Although no data indicate that IRIS worsens CMV neurologic disease syndromes, because of the localized morbidity that might occur with such an inflammatory reaction, a brief delay in initiating ART in this setting until clinical improvement occurs might be prudent (**CIII**).

Monitoring and Adverse Events, Including IRIS

Management of CMV retinitis requires close monitoring by an experienced ophthalmologist and the primary clinician. Consideration should be given to both treating the infected eye and preventing infection in the contralateral eye using systemic treatment.

Indirect ophthalmoscopy through a dilated pupil should be performed at the time of diagnosis of CMV retinitis, after completion of induction therapy, 1 month after the initiation of therapy, and monthly thereafter while the patient is on anti-CMV treatment (**AIII**). Monthly fundus photographs, using a standardized photographic technique that documents the appearance of the retina, provide the optimum method for following patients and detecting early relapse (**AIII**). For patients who have experienced immune recovery, the frequency of ophthalmologic follow-up can be decreased to every 3 months (**AIII**). Because relapse of retinitis might still occur among some patients with immune recovery, ophthalmologic follow-up might be indicated; however, the optimal timing and interval of such follow-up has not been established.

Adverse effects of ganciclovir include neutropenia, thrombocytopenia, nausea, diarrhea, and renal dysfunction. Adverse effects of foscarnet include anemia, nephrotoxicity, and electrolyte abnormalities. For patients receiving ganciclovir or foscarnet, monitoring of complete blood counts and serum electrolytes and renal function should be performed twice weekly during induction therapy and once weekly thereafter (**AIII**). Cidofovir is associated with dose-related nephrotoxicity and hypotony. For patients receiving IV cidofovir, blood urea nitrogen, creatinine, and urinalysis should be performed before each infusion; administration of the drug is contraindicated if renal dysfunction or proteinuria is detected. Even in the absence of retinitis with other CMV end-organ disease, periodic ophthalmologic examinations are needed to monitor for cidofovir-associated uveitis when this agent is used.

Immune recovery uveitis (IRU) is an ocular form of IRIS caused by an immunologic reaction to CMV, characterized by inflammation in the anterior chamber or vitreous in the setting of immune recovery after initiation of ART and is usually observed among those with a substantial rise in $CD4^+$ counts in the 4 to 12 weeks after initiation of ART. Ocular complications of uveitis include macular edema and the development of epiretinal membranes, which can cause loss of vision. Treatment usually requires periocular corticosteroids or short courses of systemic corticosteroids. Estimated response rates are 50%. One uncontrolled case series suggested that IRU (or CMV retinitis-associated IRIS) might respond to oral valganciclovir.

Management of Treatment Failure

For patients without immune recovery after initiation of ART and who are receiving chronic maintenance therapy with systemic anti-CMV drugs, relapse of retinitis is likely to occur. Although drug resistance might be responsible for some episodes of relapse, early relapse is most often caused by the limited intraocular penetration of systemically administered drugs. Because it results in greater drug levels in the eye, the placement of a ganciclovir implant in a patient who has relapsed while receiving systemic treatment (IV ganciclovir or oral valganciclovir) is generally recommended and often will control the retinitis for 6 to 8 months until the implant requires replacement (**BIII**).

When patients relapse while receiving maintenance therapy, reinduction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods, and the majority of specialists recommend this approach for initial treatment of patients who experience relapsed disease (**AII**). Changing to an alternative drug at the time of first relapse typically does not result in superior control of the retinitis but should be considered if drug resistance is suspected or if side effects or toxicities interfere with optimal courses of the initial agent (**AIII**). The combination of ganciclovir and foscarnet is usually superior to systemic therapy with either agent alone and might be considered for patients with relapsed retinitis; however, this combination of drugs is accompanied by greater toxicity (**BI**).

Although early relapse is generally not a result of resistance, later relapse often is. Because patients with resistant CMV nearly always have mutations in the CMV UL97 gene, and because a limited number of mutations are responsible for most drug resistance, susceptibility resistance testing in peripheral blood using a CMV DNA PCR assay and sequencing for CMV UL97 mutations or using a point mutation assay might be reasonable for patients who relapse on therapy. Virus in the eye and in the blood are identical in >90% of cases, so evaluating the blood for resistance is reasonable, and the detection of resistance in the blood or urine correlates with clinical behavior of the retinitis. Sequencing the UL97 gene from PCR-amplified specimens from blood can be accomplished in <48 hours, correlates well with conventional drug susceptibility testing and clinical outcomes, and, therefore, has clinical utility (**BII**) when conventional methods of culture and susceptibility testing and viral sequencing are not available or are too time consuming or costly. Conversely, CMV viral load measurements are of limited utility clinically because of their poor positive predictive value, but do have reasonable negative predictive value and might have utility in excluding resistance when sequencing is not available (**BII**). UL97 mutants usually respond to foscarnet, as do most UL54 mutants (except those associated with resistance to foscarnet).

Patients with low-level ganciclovir-resistant isolates in the eye might respond to a ganciclovir implant because of the higher local levels of ganciclovir resulting from this form of therapy. However, patients with high-level ganciclovir resistant isolates typically will not respond and will require a switch to alternative therapy.

Preventing Recurrence

After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) is recommended for life (**AI**), unless immune reconstitution occurs as a result of ART. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir or valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, parenteral cidofovir, and (for retinitis only) ganciclovir administration through intraocular implant (**AI**). Repetitive intravitreous injections of fomivirsen also have been demonstrated to be effective in randomized clinical trials, but this drug is no longer available in the U.S.

Repetitive intravitreous injections of ganciclovir, foscarnet, and cidofovir have been effective for secondary prophylaxis of CMV retinitis in uncontrolled case series. Because of the risk for hypotony and uveitis, the intravitreal administration

of cidofovir should be reserved for extraordinary cases. Intraocular therapy alone does not provide protection to the contralateral eye or to other organ systems and typically should be combined with oral valganciclovir.

The choice of a chronic maintenance regimen for patients treated for CMV disease should be made in consultation with a specialist. For patients with retinitis, this decision should be made in consultation with an ophthalmologist and should consider the anatomic location of the retinal lesion, vision in the contralateral eye, the immunologic and virologic status of the patient, and the patient's response to ART.

Patients with lesions that immediately threaten vision need prompt anti-CMV therapy because progression of the retinitis can occur during the time in which immune recovery is occurring. Patients with retinitis that immediately threatens sight still might benefit most from the use of the ganciclovir implant because of its ability to deliver high concentrations of drug locally and its superior ability to control retinitis progression (**BI**). However, replacement of the ganciclovir implant at 6 to 8 months might not be necessary for those with sustained immune recovery. If the ganciclovir implant is used, it should be combined with oral valganciclovir until immune recovery occurs (**BIII**).

Chronic maintenance therapy is not routinely recommended for gastrointestinal disease but should be considered if relapses occur (**BII**). A role for maintenance therapy for CMV pneumonitis has not been established (**CIII**).

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

Discontinuing secondary prophylaxis (chronic maintenance therapy) is reasonable for patients with a sustained (3 to 6 months) increase in $CD4^+$ counts >100 cells/microliter in response to ART (**BII**). Such decisions should be made in consultation with an ophthalmologist and should include magnitude and duration of $CD4^+$ count increase, anatomic location of the retinal lesions, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring (**BII**).

All patients who have had anti-CMV maintenance therapy discontinued should continue to undergo regular ophthalmologic monitoring for early detection of CMV relapse and for IRU, optimally every 3 months (**AIII**). Monitoring CMV viral load has poor positive predictive value for relapse of the retinitis and, therefore, is not recommended (**DII**).

Relapse of CMV retinitis occurs frequently among patients whose anti-CMV maintenance therapies have been discontinued and whose $CD4^+$ counts have decreased to <50 cells/microliter. Therefore, reinstitution of secondary prophylaxis should occur when the $CD4^+$ count has decreased to <100 cells/microliter (**AIII**).

Special Considerations During Pregnancy

The diagnostic considerations among pregnant women are the same as for the nonpregnant women. Indications for treatment of CMV infection during pregnancy are the same as for those in nonpregnant HIV-infected adults (**AIII**). For retinal

disease, use of intraocular implants or intravitreous injections for local therapy should be considered in the first trimester, if possible to limit fetal exposure to systemically administered antiviral drugs (**CIII**). Systemic antiviral therapy as discussed should then be started after the first trimester.

Ganciclovir is embryotoxic among rabbits and mice and teratogenic (i.e., cleft palate, anophthalmia, aplastic kidney and pancreas, and hydrocephalus) in rabbits. Safe use in human pregnancy after organ transplantation has been reported, and use in late pregnancy to treat fetal CMV infection in HIV-uninfected women has also been reported. Foscarnet is associated with an increase in skeletal anomalies or variants in rats and rabbits. No experience with use early in human pregnancy has been reported. A single case report of use in the third trimester described normal infant outcome. Cidofovir is embryotoxic and teratogenic (i.e., meningomyelocele and skeletal abnormalities) among rats and rabbits. No experience with use of cidofovir in human pregnancy has been reported; use in pregnancy is not recommended (**DIII**).

On the basis of limited data, toxicity reports and studies, and ease of use of the various drugs, valganciclovir is recognized as the treatment of choice during pregnancy (**BIII**). No experience has been reported with the use of valganciclovir in human pregnancy, but concerns are expected to be the same as with ganciclovir. The fetus should be monitored by fetal-movement counting in the third trimester and by periodic ultrasound monitoring after 20 weeks of gestation to look for evidence of hydrops fetalis indicating substantial anemia. Because toxicity of foscarnet is primarily renal, weekly monitoring of amniotic fluid volumes by ultrasound is recommended weekly after 20 weeks of gestation to detect oligohydramnios if foscarnet is used.

Rarely, ultrasound findings in the fetus (e.g., cerebral calcifications, abdominal and liver calcifications, hydrops, microcephaly, ventriculomegaly, ascites, and echogenic fetal bowel) might indicate the possibility of in utero CMV infection among pregnant women with CMV end-organ disease. In this case, consideration of invasive testing (i.e., amniocentesis and fetal umbilical blood sampling) must be individualized on the basis of clinical history and serologic findings, gestational age, potential risk for HIV transmission, and maternal preference. Referral to a maternal-fetal medicine specialist for evaluation, counseling, and potential further testing is recommended.

On the basis of data in HIV-uninfected women, transmission of CMV from mother to infant might occur in utero. However, symptomatic infection in the newborn is usually related to primary CMV infection in the mother during pregnancy, and because >90% of HIV-infected pregnant women are CMV antibody positive in the majority of studies, the risk for symptomatic infection in the fetus is low. Therefore, treatment of asymptomatic maternal CMV infection during pregnancy solely to prevent infant infection is not indicated (**DIII**).

Herpes Simplex Virus (HSV) Disease

Preventing Exposure

The majority of HIV-infected persons have HSV-1 and -2 infections. However, prevention of acquisition of HSV is important for those who are uninfected. HSV-

2-seronegative HIV-infected persons should ask their partners to be tested using type-specific serology before initiating sexual activity, because disclosure of HSV-2 in heterosexual HSV-2-discordant couples was associated with reduced risk for transmission of HSV-2 (**BII**). Consistent use of latex condoms reduced HSV-2 acquisition from women to men and from men to women, and their use should be encouraged for prevention of transmission of HSV-2 and other sexually transmitted pathogens (**AII**). HIV-infected persons should specifically avoid sexual contact when their partners have overt (genital or orolabial) herpetic lesions (**AII**). However, sexual transmission of HSV can occur during asymptomatic shedding. The use of suppressive antiviral therapy (valacyclovir 500 mg once daily) in persons with genital herpes reduced HSV-2 transmission to susceptible heterosexual partners by 50%; the effectiveness of this approach in reducing HSV-2 transmission from HIV-seropositive persons or to HIV-seropositive persons has not been evaluated.

Preventing Disease

The dose, duration, and efficacy of antiviral prophylaxis after exposure to HSV have not been evaluated.

Treatment of Disease

Patients with HSV infections can be treated with episodic therapy when lesions occur or with daily therapy to prevent recurrences. The management of genital HSV-2 in HIV-infected persons should include several factors, including frequency and severity of HSV recurrences, the risk for HSV-2 transmission to susceptible partners, and the potential for interactions between HIV and HSV-2 that might result in increased HIV in plasma and genital secretions. Treatment for individual recurrences does not influence the natural history of genital HSV-2 infection and does not reduce the risk for HSV-2 transmission to sex partners, a major concern of persons with genital herpes.

Patients with orolabial lesions can be treated with oral famciclovir, valacyclovir, or acyclovir for 5 to 10 days (**AII**). Severe mucocutaneous HSV lesions respond best to initial treatment with IV acyclovir (**AII**). Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed. Genital HSV infection should be treated with oral valacyclovir, famciclovir, or acyclovir for 5 to 14 days (**AI**). Short-course therapy (1, 2, or 3 days) should not be used in patients with HIV infection.

Monitoring and Adverse Events, Including IRIS

Acyclovir, valacyclovir, and famciclovir are occasionally associated with nausea or headache. No laboratory monitoring is needed in patients receiving episodic or suppressive therapy unless the patient has substantial renal impairment. For patients receiving high-dose IV acyclovir, monitoring of renal function and dose adjustment as necessary are recommended at initiation of treatment and once or twice weekly for the duration of treatment. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome has been reported among HIV-infected patients treated with high-dose (8 grams/day) valacyclovir but has not been reported at doses used for therapy of HSV infection.

Cutaneous lesions that are atypical and occasionally recalcitrant to therapy have been reported in persons initiating ART and have been attributed to IRIS.

Management of Treatment Failure

Treatment failure related to resistance to anti-HSV drugs should be suspected if lesions do not begin to resolve within 7 to 10 days after initiation of therapy. Among immunocompromised patients with suspected acyclovir-resistant HSV, viral culture of the lesion should be obtained and, if virus is isolated, susceptibility testing performed to confirm drug resistance (**AII**).

The treatment of choice for acyclovir-resistant HSV is IV foscarnet (**AI**). Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required (**CIII**).

Preventing Recurrence

Most recurrences of genital herpes can be prevented using daily anti-HSV therapy, and this is recommended for persons who have frequent or severe recurrences (**AI**). The option for suppressive therapy should be discussed with every HSV-2-infected patient. Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences (**AI**). Suppressive therapy with valacyclovir should be 500 mg twice daily in HIV-infected persons (**AI**), or twice-daily regimens with acyclovir or famciclovir should be used. Daily anti-HSV suppressive therapy in HIV-infected persons also results in a decrease in HIV concentration in plasma and anal and genital secretions. Whether this regimen results in clinical benefit or decreased infectiousness is not known.

HIV-infected patients receiving ART who have immune reconstitution often experience improvement in the frequency and severity of their clinical episodes of genital herpes. However, immune reconstitution does not reduce the frequency of genital HSV shedding.

Special Considerations During Pregnancy

Diagnosis of mucocutaneous HSV infections is the same for pregnant women as for nonpregnant women. Episodic therapy for first-episode HSV disease and for recurrences can be offered during pregnancy, but suppressive therapy is not used routinely. Visceral disease is more likely to occur during pregnancy and can be fatal. Acyclovir is the antiviral drug with the most reported experience in pregnancy and appears to be safe; therefore, acyclovir is the first choice for therapy of HSV infections in pregnancy (**AIII**).

An additional concern with HSV during pregnancy is the potential for HSV transmission to the fetus and neonate. The rate of transmission to the newborn in HSV-2-seropositive pregnant women is low, unless the pregnant woman has acquired genital HSV in late pregnancy. The predominant risk for HSV transmission is maternal genital shedding of HSV at delivery. Cesarean delivery is recommended for women with a prodrome or visible HSV genital lesions at the onset of labor (**BII**). Maternal genital herpes is a risk factor for perinatal mother-

to-child HIV transmission. Whether HSV suppression reduces the risk for HIV transmission during pregnancy, birth, or breastfeeding is unknown.

Use of acyclovir in late pregnancy suppresses genital herpes outbreaks and reduces the need for Cesarean delivery for recurrent HSV in HIV-seronegative women and is likely to have similar efficacy in HIV-seropositive women (**BII**). However, the use of acyclovir in HIV-infected pregnant women to reduce the risk for intrapartum HIV and HSV transmission to the neonate has not been evaluated.

Human Herpesvirus-6 (HHV-6) and HHV-7 Disease

Preventing Exposure

HHV-6 and HHV-7 are ubiquitous universal infections, and prevention of exposure is not feasible.

Preventing Disease

Because of the ubiquity of HHV-6 and -7 during early childhood and the lack of an effective vaccine, prevention of primary HHV-6 and -7 infections or HHV-6 disease is not feasible.

Treatment of Disease

Antiviral susceptibility patterns of HHV-6 resemble those of CMV. HHV-6 replication is readily inhibited by foscarnet, cidofovir, and ganciclovir at levels that are easily achievable in the human plasma. Indications for treatment of HHV-6 infection in HIV-seropositive patients are unclear. However, if disease in an HIV-infected person is determined to be caused by HHV-6, ganciclovir or foscarnet can be considered treatment options using treatment schedules and doses similar to those used for CMV disease (**CIII**). HHV-7 has not been recognized as a cause of disease in HIV-infected persons, and no recommendation for treatment can be made.

Monitoring and Adverse Events, Including IRIS

See CMV treatment recommendations above for monitoring and adverse events. HHV-6 and -7 have not been demonstrated to be associated with IRIS.

Management of Treatment Failure

Mutations conferring resistance of HHV-6 to ganciclovir, cidofovir, and foscarnet have been described. Theoretically, treatment failures could be managed by switching classes of antiviral medications (e.g., changing from ganciclovir to foscarnet), but data are completely lacking (**CIII**).

Preventing Recurrence

No data exist on prevention of HHV-6 or HHV-7 reactivation from latency in HIV-infected patients. Use of antiviral medications for this indication is not recommended (**DIII**).

Special Considerations During Pregnancy

Given the epidemiology of HHV-6 infection, symptomatic infection and indications for treatment in pregnancy are expected to be rare. See the section "Special Considerations During Pregnancy" in the CMV section above for a discussion of concerns regarding use of ganciclovir and foscarnet in pregnancy. Treatment of HHV-7 during pregnancy is not indicated.

Varicella Zoster Virus (VZV) Disease

Preventing Exposure

HIV-infected persons who are susceptible to VZV (i.e., those who have not been vaccinated, have no history of varicella or herpes zoster, or are seronegative for VZV) should avoid exposure to persons with chickenpox or herpes zoster **(AII)**. VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent acquisition of chickenpox and potential transmission of VZV to their susceptible HIV-infected contacts (**BIII**).

Preventing Disease

Postexposure Prophylaxis

For prophylaxis against chickenpox, HIV-infected children and adults who are susceptible to VZV should receive varicella-zoster immune globulin (VariZIG™) as soon as possible (but within 96 hours) after close contact with a person who has active varicella or herpes zoster (**AIII**). As of June 2007, VariZIG can be obtained only under a treatment investigational new drug (IND); contact FFF Enterprises, 800-843-7477. The duration of protection should last at least for 3 weeks. Patients receiving monthly high-dose immune globulin intravenous (IGIV) (>400 mg/kg) are likely to be protected and probably do not require VariZIG if the last dose of IGIV was administered <3 weeks before exposure. Risk for VZV transmission is higher from exposure to a patient with chickenpox than from exposure to localized herpes zoster.

Among VZV-susceptible immunocompetent children, post-exposure varicella vaccination has been shown to reduce the risk for chickenpox developing in children and is more effective than pre-emptive therapy with acyclovir. Post-exposure varicella vaccination (for patients with CD4+ counts of >200 cells/microliter) or short-term post-exposure administration of acyclovir may be considered for preventing chickenpox among susceptible HIV-infected adolescents or adults, but has not been studied in this population (**CIII**).

Long-term–drug prophylaxis for prevention of primary VZV infection in HIV-infected persons is not recommended (**DIII**).

Vaccination

The live attenuated varicella vaccine has been documented to be safe and immunogenic in HIV-infected children aged $\geq$8 years with CD4+ counts $\geq$200 cells/microliter (CD4+ percentage is $\geq$15%) and is recommended for those

children. No studies have evaluated the vaccine in HIV-infected adolescents or adults, but varicella vaccination (two doses, administered 3 months apart) may be considered in HIV-seropositive/VZV-seronegative persons ≥8 years old with CD4+ counts ≥200 cells/microliter (**CIII**). If vaccination results in disease because of vaccine virus, therapy with acyclovir is recommended (**AIII**). Administration of varicella vaccine to more severely immunocompromised HIV-infected patients is not recommended (**DIII**). Because of the high prevalence of VZV seropositivity in adults, use of varicella vaccine in this population will be infrequent. Routine serologic testing to determine the VZV serologic status of HIV-infected adults is not recommended.

Treatment of Disease

No controlled prospective studies of antiviral therapy for chickenpox in HIV-infected adults have been reported. For uncomplicated varicella, recommended treatment options are oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily), valacyclovir (1 g PO three times daily [tid]), or famciclovir (500 mg PO tid) for 5 to 7 days (**AII**). IV acyclovir for 7 to 10 days is the recommended initial treatment for HIV-infected patients with severe chickenpox (**AIII**). If no evidence of visceral involvement with VZV is available, switching to oral antiviral therapy after the patient has defervesced may be permissible (**AIII**).

Prompt antiviral therapy should be instituted in all immunosuppressed herpes zoster patients within 1 week of rash onset or any time before full crusting of lesions. The recommended treatment options for acute localized dermatomal herpes zoster in HIV-infected patients are oral valacyclovir, famciclovir, or acyclovir for 7 to 10 days (**AII**), although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. If cutaneous lesions are extensive or if visceral involvement is suspected, IV acyclovir should be initiated and continued until clinical improvement is evident (**AII**). A switch from IV acyclovir to oral antiviral therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral VZV infection are improving (**AIII**). Because of the absence of data to support benefit in this population, adjunctive corticosteroid therapy for herpes zoster is not recommended (**DIII**).

Optimal antiviral therapy for progressive outer retinal necrosis (PORN) remains undefined. Prognosis for visual preservation in involved eyes is poor despite aggressive antiviral therapy. A treatment regimen recommended by certain specialists is a combination of IV ganciclovir and foscarnet, plus intravitreal injections of ganciclovir and/or foscarnet (**AIII**). Optimization of ART in HIV-infected patients with PORN is also recommended (**AIII**). Anecdotal reports have described success with IV cidofovir. ARN appears to be more responsive to antiviral therapy; one recommended treatment is high-dose IV acyclovir (10 mg/kg every 8 hours for 10 to 14 days), followed by prolonged oral valacyclovir (1 gram tid for 6 weeks) (**AIII**). Involvement of an experienced ophthalmologist in management of patients with VZV retinitis is strongly recommended (**AIII**).

The incidence of herpes zoster in HIV-infected adults does not appear to be affected by ART therapy. Optimization of ART is recommended in patients with VZV infections (e.g., PORN) (**AIII**) that are difficult to treat.

Monitoring and Adverse Events, Including IRIS

For monitoring and adverse event recommendations related to anti-herpesvirus drugs, see preceding sections on HSV and CMV. Providers should be aware of the increased incidence of herpes zoster after initiation of ART. Such episodes should be treated as other episodes of herpes zoster.

Immune reconstitution following initiation of ART might be associated with an increased frequency of VZV reactivation. Between 4 and 16 weeks after beginning ART, the risk for herpes zoster increases two- to fourfold from baseline. During the 6 months after the start of combination ART, the incidence of herpes zoster exceeds 90 episodes per 1,000 person years. The percentage of CD8+ lymphocytes at baseline and the magnitude of their increase at 1 month after initiation of drug therapy are strongly associated with an increased risk for herpes zoster. The clinical presentation and natural history of herpes zoster in the setting of immune reconstitution do not differ from those observed in other HIV-infected patients.

Management of Treatment Failure

Treatment failure caused by resistance of VZV to acyclovir (and related drugs) should be suspected if lesions do not improve within 10 days of initiation of therapy or if they have an atypical (e.g., verrucous) appearance. A viral culture should be obtained, and if VZV is isolated, susceptibility testing performed to confirm antiviral drug susceptibility or resistance and to document the need for alternative therapy. Among patients with suspected or proven acyclovir-resistant VZV infections, treatment with intravenous foscarnet is recommended (**AII**).

Preventing Recurrence

No intervention has been recognized as preventing the recurrence of herpes zoster among HIV-infected persons. An attenuated virus vaccine for prevention of herpes zoster has been approved for use in immunocompetent persons aged $\geq$60 years, but data regarding its use in HIV-infected persons are lacking. Prospective clinical trials to evaluate the safety and immunogenicity of herpes zoster vaccine in HIV-seropositive subjects are planned. Administration of herpes zoster vaccine to HIV-infected persons is not recommended (**DIII**).

Special Considerations During Pregnancy

HIV-infected pregnant women who are susceptible to VZV and have close contact to a person with active varicella or herpes zoster should receive VariZIG as soon as possible (within 96 hours) after exposure to VZV (**AIII**). If oral acyclovir is used for post-exposure prophylaxis, VZV serology should be performed so that the drug can be discontinued if the patient is seropositive for VZV (**CIII**). Pregnant women should not receive varicella vaccine (**EIII**).

Specific risks among HIV-infected women with varicella during pregnancy have not been reported. For HIV-seronegative women with chickenpox, the risk for transmitting VZV to the infant resulting in congenital varicella syndrome is 0.4% when infection occurs at or before 12 weeks of gestation, 2.2% with infection at 13 to 20 weeks, and is negligible after 20 weeks. Women with varicella during the first half of pregnancy should be counseled about the risks and offered detailed ultrasound surveillance for findings indicative of fetal congenital varicella syndrome. Administration of varicella-zoster immune globulin does not alter the risk for congenital varicella syndrome. Infants born to women who have chickenpox from 5 days before until 2 days after delivery should receive VariZIG to reduce the severity and mortality of neonatal varicella acquired during maternal viremia (**AIII**).

Oral acyclovir or valacyclovir are the preferred treatments for HIV-infected pregnant women who have uncomplicated chickenpox during pregnancy (**BIII**). Pregnant women who have severe varicella or who exhibit signs or symptoms of VZV pneumonitis should be hospitalized and treated with IV acyclovir (10 mg/kg every 8 hours) (**AII**).

No controlled studies of antiviral therapy of herpes zoster during pregnancy have been reported. Recommended therapy for uncomplicated shingles in pregnant HIV-infected women is oral acyclovir or valacyclovir (**BIII**).

Human Herpesvirus-8 Disease

Preventing Exposure

Recommendations related to preventing exposure to HHV-8 do not exist.

Preventing Disease

Despite observational evidence supporting a role for anti-HHV-8 therapy in preventing the development of Kaposi's sarcoma (KS), the toxicity of current anti-HHV-8 therapy outweighs the potential benefits of administration (**DIII**).

Treatment of Disease

Although ganciclovir, foscarnet, and cidofovir have in vitro activity against HHV-8, and limited studies indicate these agents might be associated with reduced KS disease progression or lesion regression, larger and more definitive studies are needed to determine whether antiviral therapy has a useful role in managing HHV-8-associated diseases. KS regression has been documented after ganciclovir or foscarnet therapy, although one study indicated cidofovir was ineffective. The use of IV ganciclovir or oral valganciclovir is, however, recommended in the treatment of MCD (**BII**) and might be useful adjunctive therapy in the treatment of primary infusion lymphoma (PEL) (**BII**). Highly active ART that suppresses HIV replication should be administered to all HIV-infected persons with KS, PEL, or MCD (**BII**), although insufficient evidence exists to support using one HAART regimen over another. Chemotherapy, in combination with ART, should be considered for patients with PEL or visceral KS (**BII**) and might be a useful adjunctive therapy in persons with widely disseminated cutaneous KS (**CIII**).

Rituximab also appears to be an effective alternative to antiviral therapy in the treatment of MCD (**BII**).

Monitoring and Adverse Events, Including IRIS

Fatal IRIS has been reported in persons initiating ART with pre-existing KS and MCD. The frequency of HHV-8-associated IRIS is not known but suppression of HIV replication and immune reconstitution are key components of therapy and initiation of ART should not be delayed.

Preventing Recurrence

Effective suppression of HIV replication with ART among HIV-infected patients with KS might prevent KS progression or occurrence of new lesions and should be considered for all persons with evidence of active KS (**BII**). Suppression of HIV replication also is recommended for persons with MCD (**BII**) and those with malignant lymphoproliferative disorders.

Special Considerations During Pregnancy

HHV-8 seropositivity does not appear to impact pregnancy outcome. Routine screening for HHV-8 by PCR or serology is not indicated for HIV-infected pregnant women (**DII**). In vitro models suggest that beta-human chorionic gonadotropin induces regression of KS tumors, but clinical reports on the incidence and natural history of KS in pregnancy are conflicting.

Diagnosis of KS or other HHV-8-associated neoplasms in pregnancy should be the same as among nonpregnant women. Recommendations for the treatment of HHV-8 malignancies are beyond the scope of these guidelines. Treatment should be undertaken in consultation with a specialist.

Perinatal transmission of HHV-8 might occur infrequently. Evidence supporting vertical transmission during pregnancy or the intrapartum period includes cases of KS occurring in the infant shortly after birth, higher risk for transmission with higher maternal antibody titer (and by inference higher maternal levels of HHV-8), and detection of similar strains of HHV-8 DNA by PCR in specimens drawn at birth from HHV-8-seropositive mothers and their infants. Data indicate increased mortality through 24 months among HIV-infected infants born to HHV-8 seropositive compared with HHV-8 seronegative mothers, but these studies could not completely account for other confounding factors affecting HIV-infected infants. The majority of studies document a substantially higher rate of HHV-8 seropositivity among children born to HHV-8 antibody-positive compared with HHV-8 antibody-negative women.

Human Papillomavirus (HPV) Disease

Preventing Exposure

Consistent and correct use of male latex condoms has been associated with 72% reduction in risk for acquisition of genital HPV infection among sexually active college age women. Evidence confirms that condom use might reduce the risk for

HPV-associated disease, including warts, cervical cancer, and CIN in women. Fewer data are available on prevention of HPV infection and HPV-associated conditions among HIV-seropositive patients. Laboratory studies have indicated that latex condoms provide a sufficient barrier to prevent passage of particles the size of HPV. Although condoms might not prevent transmission of HPV from skin outside the area of condom coverage, they should be used by sexually active HIV-seropositive patients to reduce the risk for transmission or acquisition of sexually transmitted infections (**AII**).

A vaccine targeted against HPV16 and HPV18 (the two HPV types responsible for 60% to 70% of cervical cancers) and HPV6 and HPV11 (which cause most anogenital warts) was licensed and recommended for use in 2006. This quadrivalent HPV vaccine was efficacious in preventing HPV infection and high-grade CIN associated with vaccine-related HPV types among young HIV-seronegative women. A second vaccine targeting HPV16 and 18 has had similar efficacy. No data are available regarding the safety, tolerability, immunogenicity, or efficacy in HIV-infected women, and specific recommendations for HIV-seropositive women await data from ongoing studies. However, given the safety of other noninfectious vaccines in HIV-seropositive patients, the HPV vaccine is not absolutely contraindicated in HIV-seropositive women, and it may be used in circumstances when the clinician believes clinical benefit can be derived. The HPV vaccine has not demonstrated therapeutic benefit to treat existing HPV-related lesions in either HIV-seropositive or HIV-seronegative women, and women who have already acquired one sexually transmitted infection (e.g., HIV infection) are presumably more likely to have acquired others (e.g., infections with various HPV types). No published studies support using the HPV vaccine to prevent HPV infection and associated lesions of the anus, penis, or oral cavity; the vaccine is not currently approved for use in men in the U.S. As in HIV-seropositive women, no data on the safety or efficacy of the HPV vaccine in HIV-positive men are available.

Preventing Disease

Preventing Cervical Cancer

See the guidelines in the original guideline document for the use of cytology and biopsy to diagnose CIN. Also see the section regarding treatment of CIN below.

After obtaining a complete medical history, including the history of previous cervical disease, HIV-seropositive women should have a pelvic examination and a Papanicolaou (Pap) test. The Pap test should be obtained twice during the first year after diagnosis of HIV infection and, if the results are normal, annually thereafter (**AII**). If the results of the Pap test are abnormal, care should be provided according to the National Guideline Clearinghouse (NGC) summary of the American Society for Colposcopy and Cervical Pathology (ASCCP) 2001 Consensus Guidelines for Management of Women with Cervical Intraepithelial Neoplasia.

Regardless of CD4+ count, plasma HIV viral load, or antiretroviral treatment status, colposcopy and appropriate directed biopsy are recommended for HIV-seropositive women with cytological reports of "atypical squamous cells, cannot exclude high grade squamous intraepithelial lesion" (ASC-H), (**BII**), low-grade squamous intraepithelial lesion (LSIL)(**AII**), high-grade squamous intraepithelial

lesion (HSIL)(**AII**), or squamous cell carcinoma (**AII**). HPV testing may be used in the management of HIV-seronegative women with a cytologic diagnosis of atypical squamous cell of undetermined significance (ASC-US). This has been recommended for similar use in HIV-seropositive women in recent ASCCP guidelines. However, published data are limited, conflicting, and insufficient to support the use of HPV DNA testing in triage of ASC-US among HIV-seropositive women (**DIII**). A prudent plan is to perform routine colposcopy for HIV-seropositive women with ASC-US (**CIII**).

Among women with ASC-US on a Pap test, if a biopsy-confirmed CIN is absent and the colposcopic exam was adequate, follow-up with cervical cytology in 12 months is recommended (**BIII**), with referral back to colposcopy if results of ASC-US or greater are obtained. After two repeated results negative for intraepithelial lesion or malignancy, an affected woman can return to routine annual cytological screening (**AII**). ASCCP guidelines should be followed if the colposcopic exam is not adequate or when CIN is found.

If no CIN 2 or 3 lesion is identified at colposcopy among women with ASC-H, and a review of the results confirms the reading of ASC-H, cytological follow-up is recommended at 6 and 12 months (**CIII**). Women with ASC-US or greater on repeat cytology should again be referred for repeat colposcopy (**BII**).

For women referred to colposcopy for LSIL, if the colposcopy is satisfactory (entire squamocolumnar junction can be visualized with the colposcope) and no lesion or CIN is identified, follow-up with repeat cytological testing at 6 and 12 months is recommended (**BII**). ASCCP guidelines should be followed if the colposcopy is unsatisfactory or CIN is found.

A cytological result of HSIL identifies a woman at high risk for high-grade CIN or invasive cervical cancer. An immediate loop electrosurgical excision or colposcopy with endocervical assessment is an acceptable method for managing women with HSIL (**BII**). ASCCP guidelines should be followed if the colposcopy is satisfactory and no lesion or only CIN 1 is identified, or the colposcopy is unsatisfactory, or CIN 2 or 3 is found.

Atypical glandular cells (AGC) on cytology are associated with greater risk for CIN and glandular neoplasia than ASC-US or LSIL. The Bethesda system has classified AGC into three categories: AGC, either endocervical, endometrial, or glandular cells not otherwise specified ("AGC NOS"); AGC, either endocervical or glandular cells favor neoplasia ("AGC favor neoplasia"); and endocervical adenocarcinoma in situ (AIS). Colposcopy with endocervical sampling is recommended for all the subcategories of AGC and AIS (**AII**). Endometrial sampling is recommended in conjunction with colposcopy and endocervical sampling in women 35 years of age and older (**BII**). ASCCP guidelines should be followed for women under the age of 35 and for subsequent evaluation of AGC.

For women with "AGC favor neoplasia" or AIS, those with normal colposcopy should undergo a diagnostic excisional procedure (e.g., cold knife excision, loop electrosurgical excision) (**BII**). If the initial colposcopy is normal in a woman with "AGC NOS," repeat cytology is recommended at 4- to 6-month intervals until four consecutive tests negative for intraepithelial neoplasia are obtained before returning to routine cytological screening (**BIII**). If abnormal cytology, including

ASC, is obtained on follow-up cytology, repeat colposcopic examination or referral to a specialist is recommended (**BIII**).

Preventing Vaginal and Vulvar Cancer

In keeping with recommendations for HIV-seronegative women, routine screening of HIV-seropositive women for vaginal cancer following a hysterectomy for benign disease is not recommended, but women with a history of high-grade CIN or invasive cervical cancer are at increased risk and should be followed with a regular vaginal cuff Pap test (**AIII**). For patients with abnormal vaginal cuff Pap tests with no visible vaginal colposcopic abnormalities, vaginal colposcopy and use of Lugol's iodine to stain the vagina are recommended (**AIII**). Vaginal colposcopy is also indicated in the presence of concomitant cervical and vulvar lesions. Classification of VAIN parallels that of the cervix (i.e., VAIN 1, VAIN 2, and VAIN 3).

No screening procedure is available for vulvar cancer. However, for HIV-seropositive women with a past history of cervical or VAIN/cancer, an inspection of the vulva with or without colposcopy should be encouraged as part of their regular follow-up (**CIII**). Diagnosis of VIN/cancer should be confirmed with a biopsy (**AII**). A wedge biopsy under local anesthesia is usually done.

Preventing Anal Cancer

No national recommendations exist for routine screening for anal cancer. Until such time, certain specialists recommend an annual digital rectal examination as an important procedure to detect masses on palpation that might be anal cancer (**BIII**). In addition, certain specialists recommend anal cytologic screening for HIV-seropositive men and women (**CIII**). If anal cytology is performed and indicates ASC-US or ASC-H, LSIL, or HSIL (**BIII**), then it should be followed by high-resolution anoscopy (HRA). Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer (**BIII**). See section on treatment for details of treatment of AIN.

Preventing Other HPV-Associated Cancers Among HIV-Seropositive Men and Woman

Other cancers that have been associated with HPV infection among HIV-seropositive men and women include oropharyngeal squamous cell and penile cancers. Prevention options for these cancers are unclear. Circumcision might reduce the risk for penile cancer as documented in one study; however, the benefits of circumcision to prevent HPV infection and penile cancer have not been studied in a randomized clinical trial or among HIV-seropositive men. No national recommendations exist for screening for oropharyngeal or penile cancer or precancerous lesions among those with HIV infection.

Treatment of HPV-Associated Genital and Anal Lesions

Treatment of Genital and Oral Warts

Treatments are available for genital warts, but none is uniformly effective. No single treatment has been demonstrated to be superior to any other, and no single treatment is ideal for all patients or all warts. Recurrences are common regardless of the modality. Data are limited on the response of HIV-seropositive patients to the available treatments for genital warts. In the absence of data specific to the HIV-seropositive population, guidelines for the treatment of STDs for HIV-seronegative patients should be followed. Data are insufficient to recommend a single treatment modality for all patients, and more than one treatment option might be required for refractory or recurrent lesions among patients with HIV infection.

Patient-applied treatments are generally recommended for uncomplicated external warts that can be easily identified by the patient and consist of the following options:

Podophyllotoxin (e.g., podofilox [0.5% solution or gel]) is an antimitotic agent that should be applied topically to warts twice daily for 3 days, followed by 4 days of no therapy. Treatment can be repeated weekly for up to four cycles (**BIII**). The efficacy is 40% to 60% in immunocompetent subjects.

Imiquimod (5% cream) is a topical cytokine inducer that recruits an inflammatory response to the site of the wart. Patients should apply the cream once daily at bedtime three times a week for up to 16 weeks. The treatment area should be washed with soap and water 6 to 10 hours after the application (**BII**). The efficacy of imiquimod in immunocompetent persons is 30% to 70%; the overall response in HIV-seropositive persons might be lower than in immunocompetent persons.

Provider-applied treatments are typically recommended for complex or multicentric lesions or those lesions inaccessible to patient-applied treatments. These include intra-anal and vaginal warts. Options are summarized as follows:

Cryotherapy (liquid nitrogen or cryoprobe) destroys lesions by thermal-induced cytolysis. Liquid nitrogen should be applied until each lesion is thoroughly frozen and repeated every 1 to 2 weeks. Certain specialists recommend allowing the lesion to thaw and freezing a second time in each session (**BIII**). The efficacy of cryotherapy is 60% to 80%.

Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) (80% to 90%) act as caustic agents to kill wart tissue. Providers should apply a small amount to warts only and allow them to dry, at which time a white "frosting" develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap to remove unreacted acid. The treatment can be repeated weekly for 3 to 6 weeks (**BIII**). The expected efficacy is 60% to 80%.

Surgical treatments (tangential scissor excision, tangential shave excision, curettage, electrosurgery, electrocautery, infrared coagulation) can be used for external genital and anal warts (**BIII**). Laser surgery also can be used, but is usually more expensive (**CIII**). The efficacy of surgical removal can approach 100%, depending on the location of the lesions.

Podophyllin resin is a crude extract that contains podophyllotoxin and other cytotoxins and induces wart necrosis after topical application. It is prepared as a 10% to 25% suspension in tincture of benzoin. It is applied to all lesions by the provider (up to 10 cm^2 of skin area) and then removed by washing a few hours later. Applications can be repeated weekly for 3 to 6 weeks (**CIII**). Efficacy is 20% to 80%. It is usually only applied to external lesions and use of podophyllotoxin is preferred over podophyllin resin.

Other treatments might be options, but because of limited available data, difficult administration, or possible side effects these treatments should be considered only if the treatments described above are ineffective. In limited, uncontrolled studies, topical application of cidofovir has reported activity against genital warts (**CIII**). No topical formulation is commercially available. Intralesional interferon (IFN) has been used for the treatment of genital warts but because of cost, difficult administration, and potential for systemic side effects (i.e., fever, fatigue, myalgias, and leukopenia) it is not recommended for first-line treatment (**DIII**). Among non-HIV–infected persons, the overall efficacy of IFN in treating genital warts is not superior to other therapies and it has not been specifically studied for efficacy among HIV-infected persons.

Oral warts can be located on various surfaces in the mouth. In contrast to other oral manifestations of HIV, an increased prevalence of oral warts in patients on ART has been reported from the U.S. and the United Kingdom. No randomized trials of treatment of oral warts exist. Treatments include surgical excision and cryotherapy; some topical modalities have had success.

Treatment of CIN and Cervical Cancer

HIV-infected women with CIN should be managed by a specialist. Women having undergone satisfactory colposcopy with biopsy-confirmed CIN 1 preceded by ASC-US, ASC-H, or LSIL cytology can be followed with repeat cytological assessment at 6 and 12 months (**BII**). Referral to colposcopy is indicated if follow-up shows ASC or greater (**AII**). After two consecutive negative cytology tests, annual cytologic screening can be resumed (**AII**). If CIN 1 persists for at least 2 years, either continued follow-up or treatment with excision or ablation is acceptable (**AI**). ASCCP guidelines should be followed if the colposcopy is unsatisfactory, the endocervical sampling contains CIN, or the patient has been previously treated (**AIII**). A diagnostic excisional procedure or observation with colposcopy and cytology at 6-month intervals for 1 year is acceptable for CIN 1, preceded by HSIL or AGC not otherwise specified (AGC-NOS) (**BIII**). Women with satisfactory colposcopy and biopsy-confirmed high-grade CIN can be treated with either ablation (cryotherapy, laser vaporization, electrocautery, diathermy, and cold coagulation) or excisional methods (loop electrosurgical excision procedure [LEEP], laser conization, cold knife conization) (**AI**). In patients with recurrent high-grade CIN, diagnostic excisional methods are recommended (**AII**). Hysterectomy is acceptable for treatment of recurrent/persistent biopsy-confirmed high-grade CIN (**BII**). ASCCP guidelines should be followed if colposcopy is unsatisfactory.

After treatment of high-grade CIN, follow-up with cervical cytology or combination of cervical cytology and colposcopy at 6-month intervals with at least two cytologic results of "negative for squamous intraepithelial lesion or malignancy" is

acceptable (**AI**). Annual cytology can be done thereafter. Any ASC or greater requires colposcopy (**AII**).

Invasive cervical cancer is usually treated by radical hysterectomy with lymph node dissection or by radiation therapy for advanced disease. If cone biopsy or loop excision reveals microinvasive cervical cancer with clear margins, a simple hysterectomy can be done. An alternative for women with microinvasive lesions who want to preserve their fertility is local surgical procedure such as LEEP or cone biopsy with careful follow-up.

Treatment of VIN and Vulvar Cancer and of VAIN and Vaginal Cancer

Various treatment modalities for VIN are available, including local excision, laser vaporization, or ablation. Management of vulvar cancer must be individualized in consultation with a specialist. The cornerstone of the treatment of vulvar cancer is surgery. There is no standard operation and the emphasis is on the most conservative operation consistent with curing the disease. Radical vulvectomy with "en bloc" inguinofemoral lymphadenectomy has led to a favorable prognosis but with substantial morbidity. Further studies are needed to determine the optimal combined modality treatments. Radiation is also an option for some patients. The optimal treatment recommendations for HIV-seropositive women with advanced vulvar cancer remain unclear.

Similarly, treatment of VAIN is individualized in consultation with a specialist and depends on the patient's medical condition and the location and extent of the disease. Various methods of local tissue ablation to more extensive surgery have been used to treat VAIN. Treatment options include topical 5-fluorouracil, 5% imiquimod cream, laser vaporization with CO_2 laser, and excisional procedures with electrosurgical loops or a scalpel excision. On occasion, total vaginectomy may be necessary. Radiation therapy is the treatment of choice for vaginal cancer.

Treatment of AIN and Anal Cancer

For AIN, no randomized, controlled therapeutic trials have been reported and data are insufficient to recommend a specific treatment approach. Treatment decisions are based on assessment of the size and location of the lesion and the grade of histology. The least aggressive approaches should be tried first whenever possible (**CIII**): for example, several different treatments, including topical 5-fluorouracil, photodynamic therapy, infrared coagulation, cryotherapy, laser therapy, and surgical excision, have been described in small open-label studies. In retrospective analysis, infrared coagulation has been proven to have moderate efficacy to treat AIN 2 or 3 in HIV-seropositive patients (**CIII**) and was safe and well tolerated in this population in a recent AIDS Malignancy Consortium study. No indications exist for radiation therapy for patients with AIN in the absence of evidence of invasive cancer (**EIII**).

The results of studies do not indicate that treatment for AIN should be modified for patients receiving ART. Conversely, no evidence indicates that ART should be instituted or modified for the purpose of treating AIN (**CIII**).

Treatment of anal cancer must be individualized in consultation with a specialist.

Treatment of HPV-Associated Disease at Other Sites, Including the Penis and Mouth

Penile and some oral cancers are associated with HPV infection. Treatment options do not differ between HIV-seropositive and HIV-seronegative men and women. Data suggest a more favorable prognosis among HPV-associated oropharyngeal cancers compared with non-HPV associated oropharyngeal cancers.

Monitoring and Adverse Events, Including IRIS

Monitoring is required during and after treatment of genital warts because each of the treatments has associated toxicity and recurrences are common after treatment. Patients can be monitored by physical examination for evidence of recurrence. The major toxicity of podophyllotoxin and topical podophyllin resin is local skin irritation. Also, if podophyllin is applied to a large treatment area, systemic absorption can cause nausea, vomiting, and CNS effects. The major toxicity of imiquimod is inflammation at the application site. The major toxicity of cryotherapy is local pain. The major side effects of surgical treatment for genital warts are local pain, bleeding, and secondary infection. The major adverse events associated with acid cauterization are local pain and irritation or ulceration of adjacent normal skin. Intralesional IFN can be associated with systemic toxicities of IFN, including fever, fatigue, myalgia, malaise, depression, and other influenza-like symptoms. Infrared coagulation might lead to bleeding and abscess formation.

Because risk for recurrence of CIN and cervical cancer after conventional therapy is increased among HIV-seropositive persons, patients should be followed after treatment with frequent cytologic screening and colposcopic examination according to published guidelines (**AII**). Treatment of CIN with ablative and excisional modalities can be associated with several adverse events such as pain and discomfort, intraoperative hemorrhage, postoperative hemorrhage, infection, and cervical stenosis.

Each of the treatment modalities for AIN described above is associated with adverse events, primarily pain, bleeding, ulceration, and, rarely, development of abscesses, fissures, or fistulas. Patients may be monitored for adverse events using the methods described above. Treatment of anal cancer is associated with a high rate of morbidity, even when the treatment is successful. Adverse events associated with anal cancer treatment include short-term side effects commonly associated with chemotherapy, such as neutropenia, and longer-term toxicities associated with radiation therapy, such as radiation proctitis.

IRIS has not been described in association with HPV infections.

Management of Treatment Failure

Treatment failure is defined as the persistence or recurrence of lesions after appropriate therapy. For persistent or recurrent genital warts, retreatment with any of the modalities previously described should be considered, preferably with an alternative modality to the one that previously failed (**AIII**). Genital warts often require more than one course of treatment. A repeat diagnostic excision or hysterectomy is acceptable for women with histological diagnosis or recurrent or

persistent CIN 2 or 3 (**BII**). Lesion persistence and recurrences after treatment of AIN are common. No data exist to guide the choice of treatment for recurrence of AIN, but either the original therapeutic modality or a different one may be used. Treatment of anal cancer that recurs after standard chemoradiation therapy often consists of abdominoperineal resection of the tumor.

Preventing Recurrence

HIV-seropositive women are at high risk for recurrent CIN after therapy, and HIV-seropositive men and women are at high risk for recurrent AIN. Preventing recurrence requires careful follow-up of patients after treatment. Patients should be monitored with cytologic screening according to published guidelines and, when indicated, colposcopic examination for recurrent lesions (**AI**). In one study of HIV-seropositive women treated for high-grade CIN, low-dose intravaginal 5-fluorouracil (i.e., 2 grams twice weekly for 6 months) reduced the short-term risk for recurrence. However, clinical experience with this therapy is too limited to provide a recommendation for use and no follow-up study to confirm these observations has been reported. One study documented that women receiving ART are less likely to have recurrence of CIN compared with women who are not receiving treatment, but treatment for CIN should not be considered an indication for ART.

No guidelines exist regarding frequency of monitoring after therapy and the monitoring intervals will vary depending on the treatment approach, extent of disease, and other factors. Patients with AIN can be monitored by anal cytology, standard anoscopy, HRA, and biopsy as indicated. Patients with perianal intraepithelial neoplasia can be monitored by visual inspection and biopsy as indicated. Recommendations for monitoring patients for recurrence of anal cancer after completion of therapy are the same for HIV-seropositive and HIV-seronegative persons.

No indication exists for secondary prophylaxis (chronic maintenance therapy) with any of the conventional modalities to prevent recurrence of genital warts, CIN, or AIN.

Special Considerations During Pregnancy

HIV-infected pregnant women with genital warts or anogenital HPV-related neoplasia are best managed by an interdisciplinary team of specialists (e.g., OB/GYN, infectious disease physician). Pregnancy might be associated with an increased frequency and rate of growth of genital warts. Podophyllin and podofilox should not be used during pregnancy (**EIII**). Use of podophyllin has been associated with an increased risk for fetal death in several animal models and case reports in humans, but not with congenital anomalies. No experience with imiquimod in human pregnancy has been reported; therefore, its use in pregnancy is not recommended (**DIII**). No anomalies have been observed among animals with use during pregnancy.

Other topical treatments (e.g., bichloroacetic and trichloroacetic acid) and ablative therapies (i.e., laser, cryotherapy, and excision) can be used during pregnancy.

Transmission of genital HPV6 and 11 from vaginal secretions at delivery is the presumed mechanism of early onset recurrent laryngeal papillomatosis in infants. This condition is rare but is more common among women who have genital warts at delivery. Cesarean delivery is not known to prevent this condition in infants and children. No change in obstetrical management is indicated for women with HPV infection unless extensive condylomata are present that might impede vaginal delivery or cause extensive bleeding.

For evaluation of CIN, all pregnant women should have a Pap test at their initial prenatal visit unless a normal cervical cytology result has been obtained within the past year. Cytobrush sampling can be done during pregnancy. Pregnant women with abnormal cervical cytology results should undergo colposcopy and cervical biopsy of lesions suspicious for high-grade disease or cancer (**BIII**). Endocervical curettage is unacceptable in pregnant women (**EIII**). Increased bleeding might occur with cervical biopsy during pregnancy.

Pregnant women with ASC-US can be managed the same as nonpregnant women, with the exception that it is acceptable to defer colposcopy until at least 6 weeks postpartum (**CIII**). In the absence of invasive disease, treatment of CIN is not recommended during pregnancy. Re-evaluation with cytology and colposcopy is recommended after 6 weeks postpartum. Women with CIN can deliver vaginally.

Pregnant women with suspected cervical cancer should be referred to a gynecologic oncologist for definitive diagnosis, treatment, and delivery planning. Vaginal delivery is not recommended for women with invasive cervical cancer.

The effects of treatment of AIN on pregnancy are not known. Most experts recommend deferral of diagnosis and treatment of AIN until after delivery unless a strong clinical suspicion of anal cancer exists.

Hepatitis B Virus Infection

Preventing Exposure

HIV-infected persons should be counseled about the risk for household, sexual, and needle-sharing transmission of HBV; the avoidance of behaviors associated with such transmission; and the need for any such susceptible contacts to receive hepatitis A and B vaccine as described below. As drug injection via contaminated syringes previously used by infected persons is the primary route of HBV transmission among IDUs, they should be encouraged to stop using injection drugs, preferably by entering a substance abuse treatment program (**AII**). If IDUs are unwilling or unable to discontinue the use of injection drugs, they should be advised not to share needles or drug preparation equipment to reduce the risk for transmission of HBV infection (**BII**). Access to sterile injection equipment may be facilitated through enrollment of IDUs in needle exchange programs (NEPs).

Persons considering tattooing or body-piercing should be informed of potential risks of acquiring HBV, which could be transmitted if equipment is not sterile or if proper infection control procedures are not followed **(AIII)**.

Safe-sex practices should be encouraged for all HIV-infected persons; barrier precautions (e.g., latex condoms) are recommended to reduce the risk for exposure to sexually transmitted pathogens, including HBV (**AIII**).

Preventing Disease

HIV-infected patients who do not have evidence of previous exposure to HBV should be vaccinated with hepatitis B vaccine (**AII**). Given the decreased response rate to the vaccine in the setting of HIV infection, all HIV-infected patients should have anti-hepatitis B surface antibody (HBs) titers obtained 1 month after completion of the vaccine series to document response (**BIII**). If no response is observed, revaccination should be considered (**BIII**). HBV vaccination is safe in HIV-infected patients. Transient increases in HIV RNA have been reported after HBV vaccination but do not appear to have clinical relevance.

A patient who is seropositive for anti-hepatitis B core antibody (HBc) and anti-HBs has resolved infection and does not need vaccination. However, reactivation of HBV has been observed in immunosuppressed patients. The presence of anti-HBs alone at levels of >10 IU/mL is consistent with seroprotection, usually from vaccination, and no further vaccinations are required.

Determining whether hepatitis B vaccine should be administered to patients with "isolated" anti-HBc is not clear because, in addition to a false-positive result, this pattern might signify exposure in the distant past with subsequent loss of anti-HBs or more rarely, occult HBV. One approach in this setting is to administer one dose of hepatitis B vaccine followed in 2 weeks by anti-HBs testing to determine if an anamnestic response occurs, although the overall response rate described in previous studies is low (16%). Larger studies in HIV-uninfected persons with isolated anti-HBc demonstrate that most persons mount a slow, or primary, rather than a rapid, or anamnestic, response after vaccination. The majority of HIV-infected patients with isolated anti-HBc are not immune to HBV infection and should be vaccinated with a complete primary series of hepatitis B vaccine (**BII**). Certain specialists would test for HBV DNA to rule out occult chronic HBV infection before administering a complete primary series of hepatitis B vaccine.

On the basis of clinical data, early vaccination is recommended in HIV-infected patients before the CD4+ count declines to <350 cells/microliter (**AII**). However, vaccination should not be deferred for those with negative or indeterminate serologies while awaiting a rise in CD4+ count to >350 cells/microliter. Because some HIV-infected patients with CD4+ counts <200 cells/microliters do respond to vaccination, vaccination should be performed as previously recommended (**AII**), with testing for anti-HBs 1 month after completion of the series (**BIII**). If no response occurs, revaccination should be considered (**BIII**). Certain specialists might delay revaccination until after a sustained increase in CD4+ count is achieved on ART.

One study has suggested that HIV-infected persons with a CD4+ count >350 cells/microliter had improved responses when vaccinated with 40 mcg of HBV vaccine on a 0-, 1-, and 6-month schedule. Thus, certain specialists recommend initial hepatitis B vaccination in any HIV-infected person with 40 microgram doses of either vaccine at the recommended intervals (**CIII**). Additional studies are needed to determine optimal vaccination strategies in patients with advanced

immunosuppression. ART should be optimized to attain complete suppression of HIV replication and increased CD4+ count, as these factors have been associated with better antibody responses to HBV vaccination (**CIII**). Trials of immunomodulatory agents to improve HBV vaccine responses have led to mixed results, and data are currently insufficient to warrant a recommendation favoring their use (**CIII**).

No vaccination strategy has been consistently effective or adequately studied in vaccine nonresponders. For patients who have not attained an anti-HBs level >10 IU/mL after completion of a primary vaccine series, a second vaccine series is recommended (**BIII**). Certain specialists recommend that in such cases, revaccination with 40 microgram doses of either of the available vaccines be considered, regardless of which dose was used initially (**CIII**). Anti-HBs should be obtained approximately 1 month after completion of the vaccine series to assess vaccine response (**BIII**). Certain specialists suggest once yearly evaluations for patients who have an ongoing risk for HBV acquisition (**CIII**), as recommended for dialysis patients. This is particularly important in patients who have a low level of protective antibody, because loss of antibody over time is related to the maximal antibody response after vaccination, and loss of antibody among dialysis patients has translated into loss of protection against HBV infection. Immune-competent hepatitis B vaccine responders, however, remain protected against the development of clinical disease and chronic HBV infection despite subsequent declines in anti-HBs to <10 IU/mL.

Hepatitis A vaccination is recommended in persons with chronic liver disease, MSM, and IDUs. Hepatitis A virus (HAV)-susceptible, HIV-infected persons with risk factors for HAV infection should receive hepatitis A vaccination (**AII**). As with hepatitis B vaccination, the response to hepatitis A vaccination is reduced in those with CD4+ counts <200 cells/microliter. Certain specialists might delay hepatitis A vaccination until the CD4+ count is >200 cells/microliter on ART (**CIII**). Antibody response should be assessed 1 month after vaccination; nonresponders should be revaccinated (**BIII**).

Treatment of Disease

Patients with chronic hepatitis B disease should be advised to avoid or limit alcohol consumption because of its effects on the liver (**AIII**). In addition, they should be counseled about the risk for household, sexual, and needle-sharing transmission and the need for such susceptible contacts to receive hepatitis A and B vaccine as described above.

The goals of anti-HBV therapy are to prevent disease progression and reduce HBV-related morbidity and mortality. Treated patients rarely become HBsAg-negative because HBV reservoirs generally are not sufficiently reduced by available anti-HBV therapy. HBV might persist in the liver, in the absence of circulating virus, as closed circular DNA (ccDNA), which can lead to reactivation after chemotherapy, steroid use, or immunosuppression, including HIV-associated immunosuppression. Nevertheless, studies in HBV-monoinfected patients suggest suppression of HBV DNA to a "nonreplicative" state, hepatitis B e antigen (HBeAg) seroconversion from positive to negative, seroconversion to anti-HBe, loss of HBsAg, and acquisition of anti-HBs are all associated with decreased incidence of hepatocellular carcinoma (HCC) and improved survival; thus, these surrogates

also are goals of anti-HBV treatment for HIV-infected persons. For HBeAg-negative patients with increased alanine aminotransferase (ALT) and HBV DNA levels, long-term antiviral suppression might be indicated because treatment discontinuation has been associated with virologic relapse.

In HIV/HBV-coinfected patients, the imperative to treat depends not only on the level of HBV viremia and degree of biochemical and/or histologic disease, but also on whether the patient is initiating ART. HIV/HBV-coinfected patients initiating ART should be treated for HBV, regardless of the level of HBV DNA, either with antiviral agents active against both HIV and HBV or with antiviral agents with independent activity against each virus (**CIII**). This approach might reduce the risk for IRIS, particularly in those who have advanced immunodeficiency. If ART is not required, then initiation of treatment for HBV is the same as for HBV-monoinfected patients. Anti-HBV therapy is indicated for persons with abnormal ALT levels and HBV DNA levels >20,000 IU/mL (>10^5 copies/mL) for HBeAg-positive patients, and abnormal ALT levels with HBV DNA levels >2,000 IU/mL (>10^4 copies/mL) for HBeAg-negative patients (**CIII**). However, because of the increased rate of liver disease progression in the setting of HIV infection, certain specialists recommend treatment at any level of detectable HBV DNA, especially in the setting of elevated ALT levels (**CIII**). In addition, anti-HBV treatment should be considered for HIV-infected patients with low but detectable HBV DNA levels who have substantial histologic inflammatory activity or fibrosis on liver biopsy (**CIII**). Certain specialists recommend treatment of those with advanced fibrosis or cirrhosis on liver biopsy with any detectable HBV DNA level, provided other causes for chronic liver disease have been eliminated.

Treatment options for HBV in the setting of HIV infection must consider the goals of therapy and the effect treatment might have on both HIV and HBV replication. FDA-approved antiviral drugs available for treatment of HBV infection include lamivudine, adefovir, entecavir, tenofovir, standard IFN-alfa, pegylated IFN (pegIFN)-alfa, and telbivudine. FDA-approved HIV antiretroviral medications, such as emtricitabine (and its single-pill combination with tenofovir), also have substantial activity against HBV, although they are not approved for this indication.

PegIFN alfa-2a might be considered for treatment of HBV infection in HIV-coinfected patients irrespective of the need for ART for treatment of their HIV infection (**CIII**).

Because lamivudine is active against both HBV and HIV and monotherapy for HBV will select for HIV resistance mutations, lamivudine should not be used for treatment of HBV in HIV-infected patients who are not also being treated with combination ART for their HIV infection (**EIII**).

Emtricitabine is active against HBV and HIV. Because of its structural similarities to lamivudine, emtricitabine also is associated with a relatively rapid onset of HBV and HIV drug resistance, and cross resistance of HIV and HBV to lamivudine also should be assumed in patients with suspected lamivudine resistance. As with lamivudine, emtricitabine should not be used for treatment of HBV in coinfected patients who are not being treated with combination ART for their HIV infection (**EIII**).

Adefovir might be considered for treatment of HBV in HIV-coinfected patients, irrespective of the need for their HIV infection. (**CIII**).

As with lamivudine and emtricitabine, tenofovir should not be used for treatment of HBV in HIV-coinfected patients who are not receiving combination ART for treatment of their HIV infection because of the risk for acquiring HIV-associated resistance mutations (**EII**).

Entecavir should not be used as monotherapy for treatment of HBV in HIV-coinfected patients who are not also receiving combination ART for treatment of their HIV infection because of the risk for developing HIV-associated resistance mutations (**EII**).

Telbivudine has demonstrated efficacy in patients with HBeAg-positive and HBeAg-negative infection and is FDA approved for treatment of chronic HBV infection. It is well tolerated, but like lamivudine, emergence of HBV resistance over time is common. Telbivudine is not active against lamivudine-resistant HBV. Therefore, telbivudine monotherapy is not recommended (**DII**). No clinical data are currently available in HIV/HBV-coinfected patients, but studies are in progress.

Famciclovir is less active than lamivudine against HBV and is not active in lamivudine-resistant HBV; therefore, its use is not recommended (**DII**).

Treatment of HBV in HIV-Infected Patients Who Are Receiving ART

Current guidelines recommend ART for HIV-infected patients who require treatment for HBV infection, regardless of CD4+ count. In such patients, simplifying the treatment regimen can be achieved by offering at least two agents with dual activity against HIV and HBV, considering that a third agent is also required for effective treatment of HIV.

For HIV-infected persons, certain specialists recommend combination therapy with two agents active against HBV to reduce the risk for HBV drug resistance, although no results from controlled trials exist to support this strategy (**CII**). Certain specialists recommend combination therapy with emtricitabine and tenofovir as part of an ART regimen because of ease of administration, tolerability, and dual HBV and HIV activity (**CIII**). Initiation of combination therapy also avoids the administration of sequential monotherapy, which can lead to multi-drug HBV resistance over time. The combination of lamivudine and pegIFN is not superior to pegIFN alone and is usually not recommended. The strategy of combination therapy versus monotherapy for treatment of HBV is being evaluated in a comparative clinical trial.

Entecavir also can be considered in patients with complete HIV suppression who do not demonstrate tyrosine-methionine-aspartate-aspartate (YMDD) motif (M204V/I) mutations in HBV DNA (**CIII**). If entecavir is used in the presence of the M204V/I mutation, then careful monitoring of HBV DNA levels is indicated because of the increased risk for entecavir resistance in the presence of these pre-existing mutations.

Dual HBV and HCV infections are seen in 3% to 5% of HIV-infected persons. The replication of one virus usually predominates over another; this phenomenon is referred to as "viral interference." A thorough laboratory evaluation to detect dual HBV and HCV coinfection should include HBV DNA and HCV RNA assays. Among patients infected with HBV, HCV, and HIV, consideration of ART should be the first priority. If ART is administered, then anti-HBV therapy must be included as part of the regimen (as above) and anti-HCV therapy can be introduced as needed. If ART is not desired, IFN-based therapy, which suppresses both HCV and HBV, should be considered (**CIII**). If IFN-based therapy for HCV has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended (**CIII**).

Treatment of HBV in HIV-Infected Patients Who Are Not Receiving ART

For patients deferring therapy for HIV infection, agents with sole activity against HBV must be selected for treatment of chronic HBV infection (**BIII**). The lack of data regarding many of these agents in HIV/HBV-coinfected persons impedes firm treatment recommendations in this population. No data exist regarding the efficacy of pegIFN or the safety or efficacy of telbivudine in HIV-infected persons; adefovir has been evaluated in this population only in those with lamivudine-resistant HBV; and the clinical implications of entecavir-associated HIV resistance mutations prevent its use in this situation. Individualized therapy is necessary; however, certain guiding principles should be followed. The criteria for initiation of treatment for chronic HBV are the same for HIV-infected persons as for those with HBV monoinfection (**CIII**). Factors that might influence the choice of agent include the immune status of the patient, the level of hepatitis B viremia, and the patient's HBeAg status. For patients with CD4+ counts >350 cells/microliter, adefovir or pegIFN alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of HBV DNA levels and follow-up to evaluate for HBeAg seroconversion (**CIII**).

Duration of Anti-HBV Therapy

In HIV-seronegative patients, HBeAg seroconversions are sustained among approximately 80% of patients if lamivudine is continued 6 to 12 months after seroconversion. On the basis of data in HIV-uninfected persons, HIV/HBV-coinfected persons who are HBeAg positive and who become HBeAg negative and anti-HBe positive on lamivudine therapy should be treated for a minimum of 6 to 12 months beyond HBeAg seroconversion (**BIII**). All patients receiving ART should continue HBV therapy, even if they have seroconverted to anti-HBe (**CIII**).

Similar guidance on the duration of therapy can be applied to the use of other HBV active agents, with the exception of peg-IFN-based therapy, which is administered for a standard 48-week course. If HBeAg seroconversion does not occur but viral suppression has been achieved, treatment with anti-HBV agents, if tolerated, should be continued indefinitely (**CIII**).

Among HIV-seronegative, HBeAg-negative patients with chronic hepatitis B who are treated with lamivudine, ALT and HBV DNA levels might decline, but high rates of relapse have been reported when therapy is stopped. Considering these findings, a majority of specialists would continue therapy indefinitely to achieve long-term HBV viral suppression (**CIII**).

Monitoring and Adverse Events, Including IRIS

Treatment response should be monitored by testing for HBV DNA and HBeAg at 3-month intervals and at 6- to 12-month intervals after stopping treatment. A virologic response is defined as a $\geq$2 $\log_{10}$ decrease in HBV DNA after 6 months of therapy. Ideally, the HBV DNA level after 6 to 12 months is <20 to 100 IU/mL based on a real-time PCR assay. A maintained virological response is a response that continues while on therapy, and a sustained virological response is one that is still present 6 months after stopping therapy. For patients who are HBeAg positive, loss of HBeAg is also a measure of virological response. Other markers that should be monitored and indicate treatment success include improvement in liver histology based on biopsy; normalization of serum aminotransferases; and, in those with loss of HBeAg, the development of anti-HBe. Sustained loss of HBsAg is considered by some to be a complete response; however, this desirable serologic response is uncommon.

Major toxicities of IFN-alfa (pegylated or standard) include influenza-like symptoms (e.g., fever, myalgia, headache, and fatigue), neuropsychiatric abnormalities (e.g., depression, irritability, and cognitive dysfunction), cytopenias (e.g., thrombocytopenia, neutropenia, and reversible reduction in CD4+ count), retinopathy, neuropathy, and exacerbation of autoimmune disease. Depression might be severe enough to trigger suicide. Certain specialists recommend psychiatric evaluation before initiation of IFN-alfa for patients with a prior history of depression and frequent (monthly) monitoring for signs and symptoms of depression during treatment. Hypo- or hyperthyroidism, which is often irreversible, might occur 3 to 6 months after initiation of therapy with IFN-alfa. As a result, serum thyroid stimulating hormone (TSH) level should be monitored at baseline and periodically (e.g., every 3 months) for the duration of treatment. Depending on the severity of these toxicities and individual patient tolerance, side effects might be dose limiting or interfere with the ability to complete a course of treatment. IFN-alfa is contraindicated in patients with decompensated liver disease.

Adefovir causes renal tubular disease at doses of 30 mg/day or higher, but this toxicity is uncommon at the recommended 10 mg/day dose. Renal toxicity with tenofovir used solely for treatment of HBV has been reported rarely, although isolated cases of increased serum creatinine or renal tubular dysfunction have been observed, and might be more frequent in HIV-infected persons with underlying renal insufficiency or those treated for prolonged periods. Patients on either drug should have baseline urinalysis and creatinine monitoring. Periodic monitoring of serum creatinine and phosphate also should be done in patients receiving adefovir or tenofovir, especially those with underlying diabetes or taking other nephrotoxic agents, because they might be at increased risk for renal toxicity.

When anti-HBV therapy with lamivudine, adefovir, or tenofovir is initiated, discontinuation is associated with a flare of liver disease in approximately 15% of cases, with loss of the benefit accrued from previous anti-HBV treatment and possible decompensation of liver disease. Even for patients not receiving ART, certain specialists recommend that when anti-HBV therapies are initiated, they should be continued unless contraindicated or unless the patient has been treated for 6 to 12 months beyond loss of HBeAg positivity (**CIII**). However, the risks and

benefits of this practice are unknown. If anti-HBV therapy is discontinued and a flare occurs, anti-HBV therapy should be reinstituted because it can be potentially lifesaving (**BIII**).

Return of immune competence after ART (or after steroid withdrawal or chemotherapy) can lead to reactivation of HBV-associated liver disease. Any immune reconstitution can lead to a rise in serum aminotransferases, so called "hepatitis flare", which constitutes IRIS in HIV/HBV-coinfected persons. IRIS might be manifested by dramatic increases in serum aminotransferases as CD4+ counts rise within the first 6 to 12 weeks after starting ART, with signs and symptoms characteristic of acute hepatitis. After introduction of ART, serum aminotransferases should be monitored closely; some experts recommend monthly for the first 3 to 6 months and then every 3 months thereafter (**CIII**). Any association between abnormal aminotransferases and clinical jaundice or synthetic dysfunction (elevated international normalized ratio [INR] and low serum albumin) should prompt consultation with a hepatologist.

All patients with HBV and HIV must receive concomitant anti-HBV therapy when ART is used because these flares can be life threatening. Flares are worse in patients with more severe liver disease, especially cirrhosis. Distinguishing hepatotoxicity or other causes of hepatitis (acute HAV or acute HCV) from IRIS in this setting is difficult. When changing antiretroviral regimens, continuing agents with anti-HBV activity is important because of the risk for IRIS.

All classes of ARVs have been associated with hepatotoxicity as evidenced by substantial elevations in serum aminotransferases. ARV-associated hepatotoxicity might be dose dependent or idiosyncratic. The risk for hepatotoxicity has been consistently associated with elevated pre-ART aminotransferases and the presence of HBV or HCV coinfection. Despite the increased risk for hepatotoxicity in the setting of HCV or HBV coinfection, the majority of (80% to 90%) coinfected patients do not have hepatotoxicity, and clinically significant hepatotoxicity is rare; aminotransferases return to baseline in the majority of cases, even if the offending medication is continued. Therefore, discontinuing ART is probably not necessary in the presence of hepatotoxicity unless the patient has symptoms of hypersensitivity (fever, lymphadenopathy, rash), symptomatic hepatitis (nausea, vomiting, abdominal pain, or jaundice), or elevations of serum aminotransferase levels >10 times the ULN. However, the development of jaundice is associated with severe morbidity and mortality and should trigger discontinuation of the offending drug(s).

The major problem in managing adverse effects and drug-induced liver injury is determining which medication is the offending culprit and distinguishing drug toxicity from hepatic flares associated with IRIS. Close interaction of HIV clinicians and hepatologists is needed because liver histology might help to differentiate drug toxicity (e.g., eosinophils) from viral hepatitis (e.g., portal inflammation). Spontaneous HBV clearance can be associated with a flare, but occurs rarely in HIV-infected patients. Initiation of ART without anti-HBV therapy might lead to reactivation of HBV. A hepatic flare might also occur when patients must discontinue their ART. Although this should be discouraged, if ART must be discontinued for some reason, patients need to be counseled about the urgent need to continue HBV therapy but without any agents active against HIV to prevent inadvertent mono or dual anti-HIV drug selection pressure favoring

development of HIV drug resistance. Elevated aminotransferases might also occur after the onset of drug resistance, which is common and increases over time with medications such as lamivudine. Serum HBV DNA testing will help determine if a flare of HBV has occurred. In this situation, HBV resistance testing should be undertaken in consultation with a specialist. Other causes of abnormal liver tests should be sought, including drugs, alcohol, viral hepatitis, and nonalcoholic fatty liver disease.

Management of Treatment Failure

Treatment failure is defined as the presence of HBV DNA greater than 1 $\log_{10}$ above nadir in a patient who is consistently adherent to therapy. Laboratory findings associated with treatment failure include persistent ALT elevations and persistently positive HBeAg for those who had detectable HBeAg at treatment onset.

If lamivudine resistance is suspected or documented, tenofovir or adefovir should be added to lamivudine therapy (**CIII**). HBV DNA testing might be useful in this setting because increasing levels are associated with emergence of lamivudine resistance or relapse, and stable levels should suggest an alternative cause of acute deterioration. Patients receiving lamivudine who have no detectable HIV RNA, but do have detectable plasma HBV DNA, can be assumed to be lamivudine resistant. Treatment options for patients on ART who have lamivudine-resistant HBV, but fully suppressed HIV, include the addition of adefovir or pegIFN to lamivudine, or tenofovir can be exchanged for one of the nucleoside agents in the ART regimen (**CIII**). Persons with lamivudine-resistant HBV will have cross resistance to emtricitabine and telbivudine. In the setting of lamivudine-resistant HBV disease, either lamivudine or emtricitabine should be continued because this might decrease development of mutations to other anti-HBV drugs (**CIII**).

Treatment for end-stage liver disease (ESLD) among HIV/HBV-coinfected patients should be managed as it is in HIV-seronegative patients (**BI**). IFN-alfa is contraindicated in ESLD, but limited data indicate that lamivudine, adefovir, or tenofovir can be used safely. All patients with ascites should undergo paracentesis for analysis to verify that portal hypertension is the etiology and to exclude spontaneous bacterial peritonitis (SBP). Assessment of the serum-ascites albumin gradient (SAAG) is advisable; SAAG $\geq$1.1 mg/dL strongly suggests ascites secondary to portal hypertension. Management includes sodium restriction (<2 g/day) to alleviate fluid retention and diuretics. The recommended diuretic regimen is spironolactone alone or combined with furosemide (ratio of 40 mg furosemide: 100 mg spironolactone).

Consideration should be given to primary prophylaxis against SBP with the administration of oral antibiotics such as norfloxacin (400 mg/day) or TMP-SMX (1 double-strength tablet/day) in those with an ascites total protein <1 g/dL. Secondary antibiotic prophylaxis is recommended for all persons with a history of SBP (**AI**).

Esophagogastroduodenoscopy (EGD or upper endoscopy) should be performed in all persons who progress to cirrhosis, particularly those with thrombocytopenia, at the time of diagnosis and then every 1 to 2 years to identify substantial gastroesophageal varices. For persons with varices, nonselective beta blockers

(e.g., nadolol or propranolol) are the mainstay of both primary and secondary prevention of variceal hemorrhage; esophageal variceal ligation or banding is another preventive option, particularly for persons who cannot tolerate beta blockers. Hepatic encephalopathy, due to the accumulation of unmetabolized ammonia and other false neurotransmitters absorbed from the gut in the setting of liver dysfunction, might be subtle in early stages. Preventive measures include restriction of animal dietary protein consumption and the use of nonabsorbable disaccharides (e.g., lactulose) and/or antibiotics (e.g., neomycin, rifaximin).

Patients with HBV-related cirrhosis are at increased risk for HCC. Whether additional risk occurs in the setting of HIV infection is unclear. Although the optimal screening strategy to detect HCC is unknown, screening for HCC is recommended in patients with documented cirrhosis using hepatic ultrasound imaging performed at 6- to 12-month intervals (**BIII**). The utility of serum alpha-fetoprotein (AFP) for HCC screening in persons with HIV is unknown, and, because of poor specificity and sensitivity, results of AFP testing should be confirmed with liver imaging studies. In the absence of contraindications, HIV/HBV-coinfected persons with decompensated liver disease and/or early HCC are candidates for orthotopic liver transplantation because HIV infection is not a contraindication to organ transplantation with the use of effective ART. Persons with cirrhosis should undergo periodic assessment of their liver disease status through the application of validated prognostic models (Child-Pugh-Turcotte [CPT] Score and Model for End-stage Liver Disease [MELD]) that predict mortality risk and are used to determine the medical need for liver transplantation. Where feasible, coinfected persons with well-controlled HIV infection found to have liver decompensation (defined as CPT score $\geq$7 and/or MELD score >10) or evidence of early HCC should be referred for orthotopic liver transplantation (**BIII**). Because transplantation does not cure HBV infection, post-transplant HBV treatment is required (**BIII**).

Special Considerations During Pregnancy

Pregnant women, including HIV-infected women, should be screened for HBsAg. Those who are HBsAg negative and without antibody to hepatitis B should be offered vaccination against hepatitis B. This vaccination can be administered during pregnancy, preferably after the woman is on a stable ART regimen, to prevent the theoretical risk for HIV RNA rebound with vaccination. Treatment of symptomatic acute HBV infection during pregnancy should be supportive, with special attention given to maintaining blood glucose levels and normal clotting status. Risk for preterm labor and delivery might be increased with acute HBV infection.

Treatment of chronic HBV infection is usually not indicated in pregnancy (**DIII**), but HBV positivity must be taken into account when considering therapy options for the HIV-infected pregnant woman.

For women having indications for ART for their own health and expected to continue antiretrovirals postpartum, a regimen including two agents with activity against hepatitis B should be used (**AIII**). Of the antiretroviral agents with activity against hepatitis B, the one most used in pregnancy is lamivudine. Approximately 1,800 cases of pregnancy outcomes after first-trimester exposure to lamivudine have been reported to the Antiretroviral Pregnancy Registry (APR)

with no indication of an increased risk for birth defects after exposure. Lamivudine has been well tolerated by pregnant women. Tenofovir was not teratogenic in animals, but reversible bone changes at high doses were seen in multiple animal species. A total of 266 cases of first-trimester exposure have been reported to the APR with no increase in birth defects noted. Although tenofovir is not usually recommended as a first-line agent in pregnancy, in the setting of maternal chronic HBV infection, it can be included as the second agent with anti-HBV activity, in addition to lamivudine **(BIII)**. Several other antiretroviral agents with activity against HBV, including emtricitabine, adefovir, and telbivudine, have been evaluated and not found to be teratogenic in animals, but experience with these agents in human pregnancy is limited. These agents could be included in a regimen during pregnancy if other options are not appropriate. Entecavir was associated with skeletal anomalies in rats and rabbits but only at high, maternally toxic doses. Data on use of entecavir in human pregnancy are not available. Cases of exposure during pregnancy to any of the antiretrovirals and HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (800-258-4263; http://www.apregistry.com). IFNs are not recommended for use in pregnancy, and ribavirin (RBV) is contraindicated in pregnancy. Although IFNs are not teratogenic, they are abortifacient at high doses in monkeys and should not be used in pregnant women because of the direct antigrowth and antiproliferative effects of these agents.

The choice of antiretroviral regimen for the pregnant woman with chronic HBV infection who requires antiretrovirals during pregnancy only for prevention of mother-to-child transmission (MTCT) and plans to discontinue therapy after delivery is more complex. Options include starting a triple therapy regimen including two agents with activity against HBV (as discussed above) but stopping therapy after delivery and monitoring closely for a flare of HBV activity, or using a regimen not including drugs active against HBV to avoid a potential flare when discontinued. As an alternative, if only short-term therapy is planned (e.g., starting in the third trimester), consideration should be given to using a combination antiretroviral regimen using lamivudine as the sole agent with activity against HBV (**CIII**). Certain specialists recommend the first option, using a regimen with dual HBV activity. This recommendation is made even when planning to discontinue postpartum because of the concern about potential IRIS-related flare of HBV activity during pregnancy, even among women with relatively high CD4+ counts, if ARV without anti-HBV activity is used. They believe that treating a potential flare in the postpartum period after discontinuing ARV is associated with less risk than treating an immune-mediated flare during pregnancy. In addition, using drugs with anti-HBV activity during pregnancy will lower HBV levels and potentially decrease the risk for failure of hepatitis B immune globulin (HBIG) and hepatitis B vaccine to prevent perinatal transmission of HBV, which is increased among women with high HBV DNA levels. Certain specialists would use an antiretroviral regimen without anti-HBV activity to avoid the possibility of flare when discontinued postpartum and to avoid the use of tenofovir, a drug with limited experience with long-term use in pregnancy. Certain specialists would use a highly active regimen that includes lamivudine as the only antiretroviral agent with activity against HBV, especially if starting the regimen later in pregnancy because of late care or delayed HIV diagnosis, to avoid use of tenofovir while still treating HBV. Decisions regarding choice of ARV regimen should be made taking into account CD4+ count, HIV RNA levels, time needed for chronic HIV therapy, HBV levels and indications for HBV therapy, gestational age when starting therapy, and patient preference.

Infants born to HBsAg-positive women should receive HBIG and hepatitis B vaccine within 12 hours of birth (**AI**). The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively. This regimen is >95% effective in preventing HBV infection in these infants. Postvaccination testing for anti-HBs and HBsAg should be performed at age 9 to 15 months because of the infant's ongoing exposure to HBV.

Hepatitis C Virus (HCV) Infection

Preventing Exposure

The primary route of HCV transmission among IDUs is drug injection via a syringe previously used by an infected person. An increased frequency of injection, a longer duration of injection-drug use, and cocaine use are additional factors that increase the potential for HCV transmission. Strategies should be pursued to encourage IDUs to stop using injection drugs, preferably by entering a substance abuse treatment program (**AII**).

In addition to sharing syringes, other factors associated with injection, such as sharing drug solution containers, "cookers," filters, "cottons," and mixing water, also increase the likelihood of HCV transmission. If IDUs are unwilling or unable to discontinue the use of injection drugs, they should be advised not to share needles or drug preparation equipment to reduce the risk for transmission of HCV infection (**BII**). Access to sterile injection equipment can be facilitated through enrollment of IDUs in NEPs.

Persons considering tattooing or body piercing should be informed of potential risks for acquiring HCV infection, which could be transmitted if equipment is not sterile or if proper infection-control procedures are not followed (**AIII**).

Although efficiency of sexual transmission of HCV is relatively low, safe-sex practices should be encouraged for all HIV-infected persons; barrier precautions (e.g., latex condoms) are recommended to reduce the risk for exposure to sexually transmitted pathogens, including HCV (**AII**).

Preventing Disease

All HIV-infected persons should be screened for active HCV infection. HCV-seronegative persons with elevations in serum aminotransferase levels should be screened for acute infection with assays to detect HCV RNA.

Higher rates of viral clearance have been reported in HIV-infected and -uninfected persons treated with IFN-based therapy for acute HCV infection. On the basis of this information and in the absence of contraindications, acutely infected persons (<6 months from the time of HCV exposure) should be routinely offered treatment for HCV infection to prevent the development of chronic HCV infection (**BII**). The optimal time to initiate therapy for acute HCV is unknown but it might be as soon as 8 to 12 weeks after acquisition of the infection (see Treatment of Disease below).

Chronically infected persons should be counseled about methods to prevent liver damage and HCV transmission, evaluated for chronic liver disease, and considered for treatment of HCV infection. All HIV/HCV-coinfected patients should be offered antiviral treatment to prevent development of HCV-related liver disease complications (**AI**). All HIV-infected patients with HCV coinfection should be advised to avoid or limit alcohol consumption (**AII**) because alcohol ingestion, particularly in quantities greater than 20 to 50 grams (approximately 2 to 5 drinks) per day, might accelerate the progression of liver disease. Enrollment of active substance abusers into drug and/or alcohol treatment programs is strongly recommended. Persons with liver disease should limit ingestion of potentially hepatotoxic medications (e.g., acetaminophen <2 grams/day). Because iron overload might worsen liver disease, patients should avoid iron supplementation in the absence of documented iron deficiency.

Because of its increased morbidity, HIV-infected persons who are coinfected with HCV should be tested for previous or concurrent HBV infection. Despite evidence of decreased response to hepatitis B vaccine in immunosuppressed persons, those without previous HBV infection should be vaccinated. Likewise, because acute HAV infection is more likely to be fulminant in persons with underlying hepatitis, HAV-susceptible HIV-infected persons with risk factors for HAV infection should receive hepatitis A vaccination (**AII**). As with hepatitis B vaccination, the response to hepatitis A vaccination is reduced in those with CD4+ counts <200 cells/microliter. Certain specialists recommend delaying hepatitis A vaccination until the CD4+ count is >200 cells/microliter on ART (**BIII**). Antibody response should be assessed 1 month after vaccination; nonresponders should be revaccinated (**BIII**).

Among coinfected persons with cirrhosis, measures to identify and prevent complications of advanced liver disease are identical to those established in persons without HIV and should be performed routinely (**BI**). All patients with ascites should undergo paracentesis for analysis to verify that portal hypertension is the etiology and to exclude infection (ascites polymorphonuclear cell count >250 cells/mL). Assessment of the SAAG is advisable; SAAG $\geq$1.1 mg/dL strongly suggests ascites secondary to portal hypertension. Management includes sodium restriction (<2 g/day) and diuretics to alleviate fluid retention. The recommended diuretic regimen is spironolactone alone or combined with furosemide (ratio of 40 mg furosemide: 100 mg spironolactone). Consideration should be given to primary prophylaxis against spontaneous bacterial peritonitis (SBP) through the administration of oral antibiotics such as norfloxacin (400 mg/day) or TMP-SMX (1 double-strength tablet/day) in those with an ascites total protein <1 g/dL. Secondary antibiotic prophylaxis is recommended for all persons with a history of SBP (**AI**). Upper endoscopy should be performed in all persons with cirrhosis, particularly those with thrombocytopenia, at the time of diagnosis and then every 1 to 2 years to identify substantial varices. For persons with varices, nonselective beta blockers (e.g., nadolol or propranolol) are the mainstay of both primary and secondary prevention of variceal hemorrhage; esophageal variceal ligation or banding is another preventive option, particularly for persons who cannot tolerate beta blockers. Hepatic encephalopathy, caused by the accumulation of unmetabolized ammonia and other false neurotransmitters absorbed from the gut in the setting of liver dysfunction, might be subtle in early stages. Preventive measures include restriction of animal dietary protein consumption and the use of

nonabsorbable disaccharides (e.g., lactulose) and/or antibiotics (e.g., neomycin, rifaximin).

Patients with HCV-related cirrhosis are at increased risk for HCC. Whether there is additional risk in the setting of HIV infection is unclear. Although the optimal screening strategy to detect HCC is unknown, screening is recommended in patients with documented cirrhosis using hepatic ultrasound imaging performed at 6– to 12-month intervals (**BIII**). The utility of serum AFP for HCC screening in persons with HIV is unknown. Because of relatively poor specificity and sensitivity, results of AFP testing should be confirmed with liver imaging studies. In the absence of contraindications, HIV/HCV-coinfected persons with decompensated liver disease and/or early HCC might be candidates for orthotopic liver transplantation because HIV infection is not a contraindication to organ transplantation with the use of effective ART. Persons with cirrhosis should undergo periodic assessment of their liver disease status through the application of validated prognostic models (e.g., Model for End-Stage Liver Disease [MELD] score) that predict mortality risk and are used to determine the medical need for liver transplantation. Where feasible, HIV/HCV-coinfected persons with well-controlled HIV infection found to have liver decompensation (defined as Child-Pugh-Turcotte score $\geq$7 and/or MELD score >10) or evidence of early HCC should be referred for orthotopic liver transplantation (**BIII**).

Treatment of Disease

Antiviral treatment for HCV infection should be considered for all HIV-infected persons with acute or chronic HCV infection (**AI**). In the absence of contraindications to pegIFN or RBV, treatment for HCV infection should be offered routinely to persons in whom the potential benefits of therapy are judged to outweigh the potential risks, including (but not limited to) persons with the following conditions (**BII**):

- HCV genotype 2 or 3 infection
- HCV genotype 1 infection with a low HCV RNA level (<800,000 IU/mL) (although certain specialists might not recommend treatment of patients with HCV genotype 1 infection and low or intermittently undetectable HCV RNA, response to pegIFN plus RBV is improved in those with HCV RNA levels <800,000 IU/mL compared with those with levels above this threshold, which might favor treatment in this group)
- Significant hepatic fibrosis (bridging fibrosis or cirrhosis)
- Stable HIV infection not requiring ART
- Acute HCV infection (<6 months' duration)
- Cryoglobulinemic vasculitis
- Cryoglobulinemic membranoproliferative glomerulonephritis
- Strong motivation to treat their HCV infection

The goals of therapy include eradication of HCV infection; prevention of hepatic fibrosis progression; and, among persons with HCV-related cirrhosis, prevention of ESLD, HCC, and death. Although viral eradication is not anticipated in most treated persons, histologic and clinical benefits of therapy have been observed in the absence of virologic response.

On the basis of well-designed, randomized, controlled trials, pegIFN plus RBV is the recommended treatment for hepatitis C in HIV-infected persons (**AI**). Sustained virologic response (SVR) rates range from 14% to 29% for HCV genotype 1 infection and 43% to 73% for HCV genotypes 2 and 3 infection. Whereas fixed-dose RBV (800 mg/day) is recommended for HIV-infected persons with genotype 2 or 3 disease, the appropriate RBV dose for persons with genotype 1 disease has not been determined because the pivotal trials studied only fixed-dose RBV. Among HIV seronegative persons with genotype 1, pegIFN plus weight-based RBV (1,000 mg/day for persons weighing <75 kg; 1,200 mg for persons weighing ≥75 kg) was more effective than fixed-dose RBV. Although the efficacy of weight-based RBV has not yet been established in coinfected persons, several studies indicate that this strategy is not associated with increased risk for adverse effects (e.g., anemia). Accordingly, certain specialists recommend the use of weight-based RBV combined with pegIFN in HIV-infected persons with HCV genotype 1 disease (**AII**).

For HCV genotypes 1, 4, 5, or 6, the recommended treatment regimen is either pegIFN alfa-2a (180 micrograms) or pegIFN alfa-2b (1.5 micrograms/kg) administered by subcutaneous injection weekly plus oral RBV twice daily (<75 kg or 165 lbs body weight, 600 mg each morning and 400 mg each evening; ≥75 kg or 165 lbs body weight, 600 mg twice daily) for a total duration of 48 weeks **(AI)**. For HCV genotype 2 or 3, the recommended treatment is either pegIFN alfa-2a (180 micrograms) or pegIFN alfa-2b (1.5 micrograms/kg) administered by subcutaneous injection weekly plus oral RBV in a fixed dose of 400 mg twice daily for a total duration of 48 weeks (**AI**).

The optimal treatment regimen and duration of treatment for acute HCV in coinfected patients has not been determined. Among HIV-seronegative persons, regimens including pegIFN with or without RBV in dosing schedules described above have been administered for 24 weeks' duration with good results. Therefore, in the absence of better information, HIV-infected persons with acute HCV infection should be treated with one of the previously recommended regimens for ≥24 weeks' duration (**BIII**). Because the efficacy of shorter treatment duration has not been adequately evaluated in HIV-infected persons with acute or chronic HCV infection, the recommended duration of treatment is 48 weeks for chronic infection with all HCV genotypes, including 2 and 3 (**BII**); on the basis of this information, certain specialists would also treat HIV-infected patients with acute HCV infection for a total duration of 48 weeks.

Treatment for HCV infection with pegIFN plus RBV should NOT be routinely administered to persons in whom the potential risks of therapy are judged to outweigh the potential benefits including (but not limited to) persons with the following conditions (**DII**):

- Pregnancy, or who are not willing to use birth control
- Advanced HIV-associated immunosuppression uncontrolled on ART
- Hepatic decompensation (e.g., coagulopathy, hyperbilirubinemia, encephalopathy, ascites) because liver transplantation, where feasible, should be the primary treatment option for such patients (**CIII**)
- Severe, uncontrolled comorbid medical conditions (e.g., cancer or cardiopulmonary disease)

- Severe, active depression with suicidal ideation, although HCV treatment may be considered after the successful implementation of psychiatric care and treatment for depression
- Significant hematologic abnormality (e.g., hemoglobin <10.5 g/dL, absolute neutrophil count <1,000/microliter, platelet count <50,000/microliter), although HCV treatment may be considered after the correction of hematologic abnormalities (e.g., treatment of underlying causative conditions and/or use of hematopoietic growth factors)
- Renal insufficiency (creatinine >1.5 or creatinine clearance <50 cc/min), although in such persons, treatment with pegIFN alone may be considered
- Sarcoidosis because of increased risk for severe disease exacerbation with IFN therapy
- Active, uncontrolled autoimmune conditions (e.g., systemic lupus erythematosus [SLE] or rheumatoid arthritis) because of increased risk for severe disease exacerbation with IFN therapy

Patients with contraindications to the use of RBV (e.g., unstable cardiopulmonary disease, pre-existing anemia unresponsive to erythropoietin, renal failure, or hemoglobinopathy) can be treated with pegIFN alfa (2a or 2b) monotherapy (**AII**). However, substantially lower SVR rates are expected in persons not receiving RBV. Additionally, persons with modifiable contraindications to treatment should be reassessed at regular intervals to evaluate their candidacy for therapy. Active injection-drug use does not represent an absolute contraindication to treatment of HCV infection; treatment of active IDUs should be considered on a case-by-case basis, considering comorbid conditions, adherence to medical care, and risk for reinfection. Management of HCV-infected IDUs is enhanced by linking IDUs to drug treatment programs. Alcohol use negatively affects HCV disease progression and treatment; therefore, alcohol abstinence is strongly recommended before and during antiviral therapy. A history of alcohol abuse is not a contraindication to therapy.

Management of HCV in the Context of ART

The optimal timing of initiation of ART relative to treatment for HCV infection has not been established. Although control of HIV replication and higher CD4+ count as a result of successful ART might be associated with improved response to treatment for HCV infection, this theoretical possibility has not been demonstrated in clinical trials. In addition, data from randomized controlled trials indicate that no substantial relationship exists between pretreatment CD4+ count and higher SVR rates. Also, because persons with CD4+ counts <200 cells/microliter have usually been excluded from clinical trials, the efficacy and safety of pegIFN plus RBV has not been established in this population. Therefore, the majority of experts recommend initiation of ART and control of HIV viral replication before initiating treatment for HCV infection for HIV-coinfected patients with CD4+ counts <200 cells/microliter (**CIII**). However, limited evidence suggests that for persons unable to tolerate ART because of hepatotoxicity or who have persistently elevated serum aminotransferase levels (>2 times the ULN), treatment of HCV infection before initiating ART might reduce the risk for recurrent hepatotoxicity or progression of liver disease and should be considered in this situation, regardless of CD4+ count (**CIII**).

Monitoring and Adverse Events, Including IRIS

The most appropriate intervals with which to monitor patients for whom treatment for HCV infection is deferred (e.g., those with no or minimal fibrosis or inflammatory changes on liver biopsy) have not been determined, but because of unpredictable progression of fibrosis, even among those with limited fibrosis on initial liver biopsy, serial liver biopsies should be performed every 2 to 3 years.

Assessment of HCV RNA level is the best measure of treatment response and should be performed at baseline and after completion of the first 12 weeks of therapy for HCV infection. An early virologic response (EVR) is defined as either an undetectable HCV RNA level or a decrease of $\geq$2 $\log_{10}$, as measured by quantitative HCV RNA assays, at the end of 12 weeks of treatment. Patients who do not achieve an EVR by week 12 have a limited chance (<3%) of achieving SVR regardless of duration of therapy, and most specialists recommend that treatment should be discontinued after 12 weeks (**AI**). If an EVR is documented, treatment should be continued (**AI**) and a quantitative or qualitative HCV RNA assay should be performed at the end of 24 weeks of treatment. If HCV RNA levels are undetectable at the end of 24 weeks of treatment, therapy should be continued for a total duration of 48 weeks. If HCV RNA levels remain detectable after 24 weeks of treatment, therapy should be stopped (**AI**). An HCV RNA assay should be repeated both at the completion of 48 weeks of treatment and 24 weeks after completion of treatment (**AI**). An SVR is defined as the absence of detectable HCV RNA, using an HCV RNA assay with a lower limit of detection of at least 50 IU/mL, measured at 24 weeks after completion of treatment.

In the context of treatment monitoring, relapse is defined as the absence of detectable HCV RNA at the end of treatment that is not sustained after the discontinuation of therapy. Breakthrough is the re-emergence of detectable HCV RNA following suppression below the limit of detection despite the continuation of therapy. Virologic failure or nonresponse is defined as the failure to suppress HCV RNA below detection at any time during treatment. Certain specialists recommend the continuation of treatment despite virologic failure in persons with advanced liver fibrosis based on the observation that approximately one third of coinfected patients who underwent liver biopsy had histologic improvement in fibrosis, despite the absence of a virologic response in one trial. However, more recent data suggest this approach is ineffective and it is not recommended.

HIV-infected patients who achieve an SVR should be monitored with serial HCV RNA testing at 6 to 12 month intervals for an additional 1 to 5 years to exclude late relapse or reinfection with HCV, especially those at risk for continued exposure (**CIII**).

The major toxicities of IFN-alfa (pegylated or standard) include influenza-like symptoms (e.g., fever, myalgia, headache, and fatigue), neuropsychiatric abnormalities (e.g., depression, irritability, and cognitive dysfunction), cytopenias (e.g., thrombocytopenia and neutropenia, including a reversible reduction in CD4+ count), retinopathy, neuropathy, and exacerbation of autoimmune disease. Depression might be severe enough to trigger suicide. Depending on the severity of these toxicities and individual patient tolerance, side effects might be dose limiting or interfere with the ability to complete a course of treatment.

The major toxicities of RBV include dose-dependent hemolytic anemia, cough, and dyspepsia. RBV potentiates the intracellular activity of didanosine through

inhibition of inosine monophosphate dehydrogenase. Because the interaction of RBV and didanosine might lead to clinically significant inhibition of mitochondrial DNA polymerase gamma, resulting in severe pancreatitis, lactic acidosis and, in some patients, death, the combination of RBV and didanosine is strictly contraindicated (**EI**). Zidovudine can potentiate RBV-related anemia, and if other ARVs are available, modification of the ART regimen to remove zidovudine is recommended before treatment for HCV infection (**BII**). Persons in whom the discontinuation of zidovudine is not feasible should be monitored closely (every 2 weeks) for the new onset of severe anemia during the first 8 weeks of treatment. Studies support the use of erythropoietin for the management of clinically significant anemia during HCV treatment. The use of epoetin alfa might permit RBV doses to be optimized and has been associated with improved quality of life.

Mental health should be evaluated before initiation of therapy for HCV infection and should be monitored at regular intervals during treatment. Certain specialists recommend the use of standardized depression screening tools such as the Center for Epidemiologic Studies Depression Scale (CES-D). Adverse neuropsychiatric effects of pegIFN-alfa and RBV might be modified by the use of adjunctive agents such as antidepressants.

As with HBV coinfection, in HCV-coinfected persons, IRIS might be manifested by dramatic increases in serum aminotransferases as CD4+ counts rise within the first 6 to 12 weeks after starting ART. The signs and symptoms are characteristic of hepatitis flares. After introduction of ART, serum aminotransferases should be monitored closely; some experts recommend monthly for the first 3 to 6 months and then every 3 months thereafter. Any association between abnormal aminotransferases and clinical jaundice or synthetic dysfunction (elevated INR) should prompt consultation with a hepatologist.

In this setting, distinguishing hepatotoxicity or other causes of hepatitis (acute HAV or acute HBV infections) from IRIS is difficult. All classes of ARVs have been associated with hepatotoxicity, which might be dose-dependent or idiosyncratic. The risk for hepatotoxicity has been consistently associated with elevated pre-ART aminotransferases and the presence of HBV or HCV coinfection. Despite the increased risk for hepatotoxicity in the setting of HCV or HBV coinfection, the majority of (80% to 90%) coinfected patients do not develop hepatotoxicity, and clinically significant hepatotoxicity is rare; aminotransferases return to baseline in the majority of cases, even if the offending medication is continued. Therefore, discontinuing treatment in the presence of hepatotoxicity is probably not necessary unless the patient has symptoms of hypersensitivity (fever, lymphadenopathy, rash), symptomatic hepatitis (nausea, vomiting, abdominal pain, or jaundice), or elevations of serum aminotransferase levels >10 times the ULN. The development of jaundice is associated with severe morbidity and mortality and should trigger discontinuation of the offending drug(s). No reliable clinical or laboratory parameter is available that will distinguish hepatotoxicity from IRIS. Similarly, liver biopsy might not be diagnostic and are not recommended except in the presence of hepatotoxicity grade 4 or fulminant hepatitis. Prospective studies are evaluating the incidence of presumptive IRIS within the first 12 months of ART initiation. No studies exist to inform the optimal management of persons who experience IRIS in this setting.

Management of Treatment Failure

No data are available on which to base recommendations for treatment of HIV/HCV coinfected patients who fail to respond to initial treatment for HCV infection. Certain patients might benefit from retreatment with IFN-based regimens depending on their previous response, tolerance, and adherence to and the type of previous therapy, the potential potency of the new treatment regimen, the severity of liver disease, viral genotype, and other underlying factors that influence response. On the basis of limited data in persons with HCV monoinfection, extension of the duration of treatment with pegIFN plus RBV might enhance SVR rates in coinfected persons who experience a virologic response to HCV treatment followed by relapse after adequate therapy. For persons with advanced fibrosis (e.g., bridging fibrosis or cirrhosis) and for HIV/HCV-coinfected persons who fail to demonstrate an EVR on a pegIFN and weight-based RBV regimen, clinical trials indicate that maintenance pegIFN therapy is not associated with decreased risk for hepatic events or with slowing of liver fibrosis progression in HIV-infected and -uninfected persons. Therefore, maintenance pegIFN therapy is not recommended (**AI**).

Preventing Recurrence

For HIV/HCV coinfected patients, treatment-induced SVR appears to be durable and low rates of recurrent viremia have been observed in persons with undetectable HCV RNA >1 year after completion of therapy. Persons with HIV infection who achieve SVR should be counseled to stop using injection drugs, and those who continue to inject drugs should be counseled to use safe injection practices to prevent reinfection. Use of barrier precautions and other methods to prevent sexual transmission of HIV should be adequate to prevent reinfection with HCV via sexual practices.

Special Considerations During Pregnancy

Pregnant HIV-infected women should be tested for HCV infection to allow appropriate management for them and their infants during pregnancy and following delivery, and for their infants after birth. The treatment of chronic hepatitis C during pregnancy is contraindicated (**EIII**). Both pegIFN and RBV are contraindicated in pregnancy. Although IFNs are not teratogenic, they are abortifacient at high doses in monkeys and should not be used in pregnant women because of the direct antigrowth and antiproliferative effects of these agents.

RBV is an FDA category X drug because of its teratogenicity at low doses in multiple animal species. Defects noted in animals include limb abnormalities, craniofacial defects, exencephaly, and anophthalmia. RBV should not be used during pregnancy (**EIII**). Women of child bearing potential and men receiving RBV should be counseled about the risks and need for consistent contraceptive use during and for 6 months after completion of RBV therapy. However, inadvertent pregnancy during paternal exposure has not been associated with adverse events. Pregnancies that occur in women taking RBV should be reported to the Ribavirin Pregnancy Registry (800-593-2214 or http://www.ribavirinpregnancyregistry.com).

Evaluation of HCV-infected pregnant women, including liver biopsy, can be delayed until >3 months after delivery to allow potential pregnancy-related

changes in disease activity to resolve. Hepatitis A and hepatitis B vaccination can be administered during pregnancy.

Elective Cesarean delivery does not appear to reduce the risk for HCV transmission from mother to child in HIV-uninfected women, but might be protective against transmission of HCV among HIV-infected women. The adjusted odds for perinatal transmission of HCV with scheduled Cesarean delivery among HIV-infected, HCV-seropositive women was 0.36 (0.2–0.8) compared with other modes of delivery. However, another study was unable to confirm the protective effect of Cesarean delivery, possibly because two thirds of the women with HIV/HCV coinfection received an elective Cesarean delivery. Although elective Cesarean delivery in HIV/HCV-coinfected women might be considered based on HIV-related indications, data are insufficient to support its routine use for prevention of HCV transmission (**DIII**).

Infants born to HIV/HCV-coinfected women should be tested for HCV RNA at 2 and 6 months and for HCV antibody after 15 months of age (**CIII**).

Progressive Multifocal Leukoencephalopathy (PML) / JC Virus (JCV)

Preventing Exposure

JCV has a worldwide distribution and most persons exhibit serologic evidence of exposure by their late teens. No known way exists to prevent exposure to the virus.

Preventing Disease

JCV likely continues as a silent productive infection in the kidney in many persons, and this might increase in the presence of immunosuppression. Whether JCV is latent in the CNS or whether PML results from temporally more proximate hematogenous dissemination in those who have this disease is unknown. Protection is presumably conferred by active, effective immunosurveillance. Therefore, the only effective way to prevent disease is to prevent progressive HIV-related immunosuppression with ART (**AIII**).

Treatment of Disease

No established specific therapy exists for JCV infection or PML, and the main approach to treatment involves ART to reverse the immunosuppression that interferes with the normal host response to this virus. Treatment strategies depend on the patient's antiretroviral treatment status and its effect. Thus, in patients who have PML and who are not on therapy, ART should be started immediately (**AII**). For patients with PML who remain HIV-viremic because of antiretroviral resistance, their ART regimen should be optimized for virologic suppression (**AIII**). More problematic are patients who have PML despite successful virologic suppression while taking HAART. A recent report of patients who were treated intensively with four classes of ART (including enfuvirtide) suggested that this strategy might offer higher than anticipated survival. The effectiveness of an ART-intensification strategy in patients with undetectable plasma HIV requires further study (**CIII**). Approximately half of patients with PML

in the setting of HIV infection experience a remission after initiating effective ART. Although their neurological deficits frequently persist, disease progression in these patients remits. Some also will experience a degree of functional improvement.

Several agents have been proposed or reported anecdotally as more specific treatments for PML, but none of these has proven effective after more intensive scrutiny or more extensive study. On the basis of earlier case reports and drug inhibition of JCV in cell culture, IV and intrathecal cytarabine (cytosine arabinoside) were tested in a clinical trial, but neither exhibited clinical benefit. Therefore, treatment with cytarabine is not recommended (**DI**). Although cidofovir is not effective against JCV in cell culture, initial case reports and retrospective series described efficacy in HIV-infected and uninfected patients with PML. However, subsequent reports, including retrospective case-control studies, an open-label study of cidofovir in HIV-infected PML patients and, eventually, a meta-analysis including the patients from the four above studies demonstrated no neurological benefit. Thus, treatment with cidofovir is not recommended (**DII**).

Immunomodulatory approaches for treatment of PML also have been tried, but none has yet been studied in a prospective, controlled clinical trial. Although an initial retrospective analysis suggested that IFN-alpha might improve survival of HIV-infected patients with PML, a subsequent retrospective analysis did not demonstrate benefit beyond that afforded by ART; therefore, IFN-alpha cannot be recommended (**DIII**). A single report described failure of IFN-beta treatment of HIV-associated PML. Case reports describe improvement in PML-related neurological dysfunction or recovery in three non-HIV-infected patients who underwent transplantation for lymphoma and in one patient with myelodysplastic syndrome treated with interleukin-2. After a cell-culture study that indicated JCV replication could be inhibited by a topoisomerase inhibitor, an analogue, topotecan, was studied in a small trial. Results suggested a salutary effect in some, although likely little different from the natural course in other AIDS patients; therefore, topotecan is not recommended (**DIII**).

On the basis of a report indicating that the serotonergic 5HT2a receptor can serve as the cellular receptor for JCV in a glial cell culture system, drugs that block the 5HT2a receptor, including olanzapine, zisprasidone, mirtazapine, cyproheptadine, and risperidone, have been suggested as treatment for PML, although the rationale for this practice has been questioned. Although anecdotal reports of using 5HT2a receptor inhibitors are available, previous disappointments after case reports of "successful" treatment emphasize the need to test this strategy by formal trial. Therefore, routine use of these agents is not justified (**CIII**).

Because ART-induced immune reconstitution is associated with both onset and paradoxical worsening of PML, corticosteroids have also been advocated and sometimes empirically used—at varying dosages and durations—in the treatment of PML. This approach has been extended by some to include all cases of PML, including those with little or no demonstrable inflammatory component. However, no evidence supports the routine use of corticosteroids in HIV-related PML without an inflammatory response on neuroimaging (**DIII**). In patients with inflammatory PML, corticosteroid treatment might have a more rational basis.

Monitoring and Adverse Events, Including IRIS

Because the main approach to PML treatment is to reverse immunosuppression, patients might experience an exuberant response that can be classified as an IRIS or immune restoration disease (IRD). Because restoration of anti-JCV defenses is the objective of ART treatment in PML patients, the salutary therapeutic response and the immunopathology of IRIS might intersect and overlap in the same patient. The concern in these patients is to determine when the immune or inflammatory response is helpful and when harmful by virtue of local bystander cytotoxicity and edema that cause further injury and threaten brain displacement and herniation. The cellular immune response against JCV, mediated by CD8+ T-lymphocytes, is critical to the containment of PML progression and has been associated with a favorable clinical outcome.

However, an "excessive" response related to IRIS might be lethal as a consequence of the inflammatory reaction or, rarely, brain swelling and herniation. This inflammatory PML might be the disease phenotype on initial examination in patients who have recently begun ART or might evolve after ART has been initiated in the context of PML treatment. Corticosteroids have been used to control the local inflammatory reaction and reduce associated cerebral edema in this setting. Little published information exists to support their efficacy or, more specifically, to guide dosage and duration of this treatment. Corticosteroid treatment should be as short as possible and not overused. Mild swelling, edema, or contrast enhancement might be noted in some patients who respond favorably to ART, but most often these complications require no additional treatment if the patient is clinically stable and has no sign of impending brain herniation. However, in those with progressing clinical deficits and neuroimaging features suggesting inflammatory disease (edema, swelling, and contrast enhancement), corticosteroid treatment is justified (**BIII**). Although some have suggested stopping ART in the face of PML-IRIS, this is likely counterproductive and is not recommended (**DIII**).

Management of Treatment Failure

Because PML remission might take several weeks, no strict criteria define disease progression. However, a working definition might be continued clinical worsening and continued detection of CSF JCV at 3 months. In the case of ART treatment, the plasma HIV RNA and blood CD4+ count responses might provide ancillary predictive information. When the suppression of HIV RNA or the boost of CD4+ count fails, attention might focus on modifying ART. Augmenting ART even when plasma HIV RNA is below detection is under study. However, when HIV responds well to ART but PML continues to worsen, attempting one of the unproven and not routinely recommended therapies described above is reasonable, after all are informed of their rationale and unproven efficacy. Better treatments and their rigorous assessment are needed.

Preventing Recurrence

Patients experiencing remission of PML after ART rarely suffer a subsequent recrudescence, although no formal study of this has been undertaken. The main preventive measure, based on its role in reversing the disease, is an effective ART regimen that suppresses viremia and maintains CD4+ counts (**AII**).

Special Considerations During Pregnancy

Diagnostic evaluation for PML should be the same in pregnant women as in nonpregnant women. Therapy during pregnancy should consist of optimizing the antiretroviral regimen.

Geographic OIs of Special Consideration

Malaria

Preventing Exposure

Infection with *P. falciparum* in HIV-infected persons with low CD4+ counts and in pregnant women regardless of HIV infection status can be more severe than in other persons. Because no chemoprophylactic regimen is completely effective, HIV-infected persons with low CD4+ counts and women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with malaria transmission if possible (**AIII**). If travel to a malarious area cannot be deferred, use of an effective chemoprophylaxis regimen is essential, along with careful attention to personal protective measures to prevent mosquito bites.

Preventing Disease

In areas where malaria is endemic, strategies to prevent malaria and its consequences include vector control, prophylaxis, and intermittent preventive treatment in pregnancy. For U.S. travelers (including HIV-infected persons) to malarious areas, a combination of chemoprophylaxis and personal protective measures can be highly effective in preventing malaria. One of three drugs is recommended for prophylaxis: atovaquone-proguanil, mefloquine, or doxycycline. Recommendations for prophylaxis are the same for HIV-infected persons as for noninfected persons and are available at CDC's malaria website (**AIII**) (http://www.cdc.gov/malaria). Malaria incidence has been markedly reduced in African adults with HIV who receive cotrimoxazole (TMP-SMX) prophylaxis. A recent study of HIV-infected persons in Uganda demonstrated that malaria burden was reduced by 70% with cotrimoxazole, was then reduced a further 50% when antiretroviral drugs were provided, and finally a further 50% with provision of insecticide-treated nets. However, cotrimoxazole is not as effective an antimalarial prophylactic regimen as the antimalarials recommended (see Table 2 in the original guideline document). Therefore, HIV-infected travelers on prophylaxis with cotrimoxazole should not rely on it for chemoprophylaxis against malaria (**AIII**).

Treatment of Disease

Because *Plasmodium falciparum* malaria can progress within hours to severe disease or death, all HIV-infected persons with confirmed or suspected *P. falciparum* infections should be admitted to the hospital for evaluation, initiation of treatment, and observation of response to treatment. Ideally, antimalarial treatment should not be initiated until the diagnosis has been confirmed by laboratory investigations. However, treatment should not be delayed when malaria is strongly suspected but laboratory results are pending.

The choice of treatment is guided by the degree of parasitemia and the species of *Plasmodium* identified, the clinical status of the patient, and the likely drug susceptibility of the infecting species as determined by where the infection was acquired. Although impaired response has been noted in HIV-immunosuppressed persons treated with older antimalarials such as sulfadoxine pyrimethamine, no evidence indicates that response in these persons is impaired if currently recommended drugs are used. Therefore, for HIV-infected patients who do acquire *Plasmodium* infection, treatment recommendations are the same as for HIV-uninfected patients (**AIII**). Detailed antimalarial treatment recommendations have been reviewed recently. CDC posts current treatment recommendations on its website (http://www.cdc.gov/malaria) and has clinicians on call 24 hours to provide advice to clinicians on the diagnosis and treatment of malaria (CDC Malaria Hotline 770-488-7788 M–F 8 AM–4:30 PM ET, 770-488-7100 after hours).

Monitoring and Adverse Events, Including IRIS

Several potential drug interactions can occur between antimalarial and HIV drugs, and these have been reviewed recently. Atovaquone and doxycycline interactions with antiretroviral drugs and with drugs used to prevent and treat OIs have been summarized previously. Mefloquine in repeated doses has been observed to reduce area under the concentration-time curve and maximal plasma concentrations of ritonavir by 31% and 36%, respectively. Sufficient data are not available to suggest that dose adjustments are needed.

Quinine levels might be increased by ritonavir-containing regimens; conversely, nevirapine and efavirenz could reduce plasma quinine levels. Potential interactions can occur between ritonavir with chloroquine; however, the clinical significance of these interactions is unclear and until further data are available, no dose adjustments are recommended. Artemisinin-containing compounds such as artesunate, which are widely used for antimalarial treatment in other parts of the world, are not yet approved in the U.S. However, artesunate might soon be available for treatment of severe malaria in the U.S. through a compassionate use Investigational New Drug application. PIs and NNRTIs have the potential to affect metabolism of artemisinin-containing drugs, but the overall effect and clinical significance remain unclear. No IRIS has been described in association with malaria.

Management of Treatment Failure

Management of treatment failure for persons with HIV infection should not differ from HIV-positive patients except in terms of drug interactions and drug toxicities as noted above.

Prevention of Recurrence

Not applicable

Special Considerations During Pregnancy

Malaria in pregnancy affects both the mother and the fetus. Infection with *Plasmodium (P.) falciparum* during pregnancy can increase the mother's risk for

having severe disease and anemia and increase the risk for stillbirth, preterm birth, and low birthweight. The diagnosis of malaria in pregnant women is the same as in nonpregnant women.

For pregnant women with a diagnosis of uncomplicated malaria caused by *P. malariae*, *P. ovale*, chloroquine-sensitive *P. vivax*, and chloroquine-sensitive *P. falciparum*, prompt treatment with chloroquine is recommended. For pregnant women with a diagnosis of chloroquine-resistant *P. vivax*, treatment with quinine for 7 days is recommended (**AIII**). For pregnant women with a diagnosis of uncomplicated chloroquine-resistant *P. falciparum* malaria, prompt treatment with quinine and clindamycin is recommended.

On the basis of extensive experience with its use, chloroquine is considered the drug of choice for prophylaxis and treatment of sensitive strains of malaria in pregnancy. Although quinine at high doses has been associated with an increased risk for birth defects (especially deafness) in some animal species and humans (usually during attempted abortion), use of therapeutic doses in pregnancy is considered safe. Because of the potential for hypoglycemia, pregnant women treated with quinine and their neonates should have monitoring of glucose levels. Clindamycin use has not been associated with birth defects. Because of limited data, atovaquone-proquanil or mefloquine are not recommended for treatment in pregnancy and should be used only if quinine plus clindamycin or quinine monotherapy is not available or not tolerated. Animal data and human data on use of prophylactic doses of mefloquine do not suggest teratogenicity. Tetracyclines are not recommended in pregnancy because of increased risk for maternal hepatotoxicity and staining of fetal teeth and bones. Primaquine use during pregnancy is not recommended because of limited experience with its use and the potential for fetal G6PD deficiency. Artesunates are not available in the U.S.

After treatment, all pregnant women with *P. vivax* and *P. ovale* should be administered chloroquine prophylaxis for the duration of the pregnancy to avoid relapses. For pregnant women with *P. vivax* acquired in an area with chloroquine-resistant strains, once-weekly mefloquine can be used for prophylaxis. Women can be treated with primaquine after delivery if they have a normal G6PD screening test.

Penicilliosis *marneffei*

Preventing Exposure

Available information does not support specific recommendations regarding exposure avoidance. However, patients with advanced HIV disease should avoid visiting the disease-endemic areas (**BIII**).

Preventing Disease

Not applicable to residents of the U.S.

Treatment of Disease

Penicillium marneffei is highly susceptible to miconazole, itraconazole, ketoconazole, and 5-flucytosine. Amphotericin B has intermediate antifungal activity, whereas fluconazole is the least active. The recommended treatment is amphotericin B in a dose of 0.6 mg/kg body weight/day administered intravenously for 2 weeks, followed by oral itraconazole in a dose of 400 mg/day for a subsequent duration of 10 weeks (**AII**). Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for 8 weeks (**BII**), followed by 200 mg/day for prevention of recurrence. Itraconazole capsule is better absorbed when it is taken with or immediately after a meal. Itraconazole oral solution could be taken on an empty stomach. ART should be administered in accordance with standards of care in the community; consideration should be given to simultaneous administration of treatment for penicilliosis and initiation of ART to improve outcome (**CIII**).

Monitoring and Adverse Events, Including IRIS

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Preinfusion administration of 500 mL of normal saline appears to reduce the risk for nephrotoxicity during treatment. Infusion-related adverse reactions might be ameliorated by pretreatment with acetaminophen and diphenhydramine; in rare cases, glucocorticosteroids administered approximately 30 minutes before the infusion might be required (**CIII**).

Because absorption of itraconazole can be erratic, serum itraconazole levels should be obtained once in all patients to ensure adequate absorption (**AIII**). The serum concentration should be >1 micrograms/mL, ideally drawn for reasons of consistency as a trough level after at least 7 days on the current regimen. Itraconazole solution is recommended over the capsule formulation because absorption is improved, but this has not been studied specifically in HIV-infected patients.

The immune restoration inflammatory syndrome has been reported uncommonly in patients with penicilliosis. It usually occurs within a few weeks or months after starting ART, suggesting a possibility of immune reconstitution unmasking active disease. ART should not be withheld because of concern for the possible development of IRIS (**AIII**). In patients with severely symptomatic IRIS, short-course glucocorticosteroids are recommended by certain specialists (**BIII**). Delaying the initiation of potent ART until the end of the first 2 weeks of induction therapy for penicilliosis might be prudent (**CIII**).

Management of Treatment Failure

Alternative treatment options for penicilliosis are not established. A small case series reported good outcomes with voriconazole. For those whose initial therapy failed, the approach to treatment should consist of reinitiating parenteral amphotericin B followed by another course of oral itraconazole, coupled with optimizing ART, addressing obstacles to adherence, avoiding adverse drug interactions, and ensuring that adequate absorption and serum concentrations of itraconazole are achieved (**AIII**).

Preventing Recurrence

All patients who successfully complete treatment for penicilliosis should be administered secondary prophylaxis (chronic maintenance therapy) with oral itraconazole in a dose of 200 mg/day (**AI**).

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

Discontinuing secondary prophylaxis for penicilliosis is recommended for AIDS patients who receive combination ART and have CD4+ count >100 cells/microliter for ≥6 months(**BII**). Secondary prophylaxis should be reintroduced if the CD4+ count decreases to <100 cells/microliter (**AIII**) or if penicilliosis recurs at a CD4+ count of >100 cells/microliter (**CIII**).

Special Considerations During Pregnancy

The diagnosis and treatment of penicilliosis during pregnancy are similar to those in nonpregnant women with the following considerations regarding antifungal use in pregnancy. Because of their risk for teratogenicity, azoles should not be used during the first trimester of pregnancy (**EII**) (See "Mucocutaneous Candidiasis" above). Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Leishmaniasis

Preventing Exposure

Primary prevention of leishmanial infection relies on reservoir host control in areas with zoonotic transmission; vector control activities, such as indoor residual spraying and/or insecticide-treated nets; and measures to decrease transmission of infectious agents in IDUs, such as NEPs. For North American residents, these measures are only relevant during travel.

Preventing Disease

Not applicable

Treatment of Disease

Liposomal amphotericin B is the only agent approved by the FDA for the treatment of visceral leishmaniasis. Pentavalent antimony is the most widely used treatment for leishmaniasis in many parts of the world and remains the first-line treatment for cutaneous leishmaniasis caused by most species in otherwise healthy patients.

For HIV-visceral leishmaniasis-coinfected patients, the efficacy of conventional and lipid-associated formulations of amphotericin B appears to be similar to that of pentavalent antimony. However, liposomal and lipid complex preparations are substantially better tolerated than conventional amphotericin B or pentavalent antimony. The equivalent efficacy and better toxicity profile have led most clinicians to regard liposomal amphotericin B as the drug of choice for visceral leishmaniasis in HIV-coinfected patients (**AII**). The optimal amphotericin B dosage has not been determined. Regimens with efficacy include conventional

amphotericin B 0.5 to 1.0 mg/kg body weight/day IV to achieve a total dose of 1.5 to 2.0 grams (**BII**), or liposomal or lipid complex preparations of 2 to 4 mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1–5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight (**BII**). A higher daily dosage is recommended for liposomal or lipid complex (ABLC) preparations than for conventional amphotericin B (**BII**).

Few systematic data are available on the efficacy of treatment for cutaneous, mucocutaneous, or diffuse cutaneous leishmaniasis in HIV-coinfected patients. On the basis of data in HIV-negative patients with cutaneous leishmaniasis and case reports in HIV-coinfected patients, first-line treatments include liposomal amphotericin B (**BIII**), as outlined above, and pentavalent antimony (sodium stibogluconate, which is available in the U.S. through CDC, and meglumine antimoniate), 20 mg/kg body weight/day, by IV or IM route for 3 to 4 weeks depending on the form of the disease and the clinical response (**BIII**). Pentavalent antimony was recently demonstrated to increase viral transcription and HIV replication in cultures of human peripheral blood mononuclear cells, raising concerns about its use in coinfected patients. A first-line parenteral treatment should be used for mucocutaneous and disseminated cutaneous disease and for localized cutaneous disease caused by *L. braziliensis*, the species most likely to cause mucocutaneous disease. Potential second-line alternatives for cutaneous leishmaniasis include miltefosine, topical paromomycin, intralesional pentavalent antimony, and local heat therapy; however, the effectiveness of these modalities is dependent on the infecting species of *Leishmania*.

Second-line treatment options for visceral leishmaniasis in HIV-coinfected patients include miltefosine and paromomycin. Miltefosine is an oral antileishmanial agent currently available in Germany, India, and several Latin American countries; cure rates of visceral leishmaniasis in HIV-negative patients are reported to be approximately 95%. The adult dose is 100 mg daily for 4 weeks. Although data to support its use among HIV-coinfected persons are limited, it is available for the treatment of visceral leishmaniasis in Europe under a compassionate use protocol (**CIII**). Gastrointestinal side effects are the most common adverse effects but rarely limit treatment. Data from an Ethiopian population with a high prevalence of HIV-coinfection suggest that use of miltefosine was associated with a somewhat lower visceral leishmaniasis cure rate, but substantially lower mortality than pentavalent antimony. Miltefosine is teratogenic in experimental models, and its use in women of reproductive age requires a negative pregnancy test and effective contraception during and for at least 2 months after therapy. Paromomycin, a parenteral aminoglycoside, has been shown to be effective and safe in HIV-negative visceral leishmaniasis patients in India and is now in use in several countries (**BI**).

Pentamidine isethionate has been used as a second-line alternative but is no longer recommended, because of toxicity that sometimes includes irreversible insulin-dependent diabetes mellitus (**DIII**).

ART should be initiated or optimized following standard practice for HIV-infected patients (**AII**). Appropriate use of ART has substantially improved the survival of coinfected patients in Europe and decreases the likelihood of relapse after antileishmanial therapy. Immunotherapy, including IFN-gamma and recombinant

human granulocyte macrophage colony stimulating factor, has been used experimentally as an adjunct to antileishmanial treatment for refractory cases. However, a clinical trial of pentavalent antimony plus IFN-gamma for visceral leishmaniasis in HIV-coinfected patients was suspended when an interim analysis indicated that there was no advantage over pentavalent antimony alone. In addition, the use of IFN-gamma was reported to be associated with acceleration of KS in two patients with visceral leishmaniasis and HIV coinfection.

Monitoring and Adverse Events, Including IRIS

Patients receiving pentavalent antimonials should be monitored closely for adverse reactions, which are frequent and vary from mild phlebitis to death. Overall, at a dose of 20 mg/kg bodyweight/day, >60% of patients might have one or more of the following reactions: thrombophlebitis, anorexia, myalgia, arthralgia, abdominal pain, elevation of liver transaminases, amylase or lipase, and in some patients, clinical pancreatitis. Occasional electrocardiographic changes might be observed (e.g., prolonged QT intervals and T-wave inversion). Rarely, arrhythmias and sudden death have occurred. Severe adverse reactions to pentavalent antimony, including acute pancreatitis and leukopenia, appear to be more frequent in coinfected patients than in those without HIV.

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity, electrolyte disturbances, and infusion-related adverse reactions, which might be ameliorated by pretreatment with acetaminophen, diphenhydramine, or limited doses of corticosteroids (**CIII**). Previous fluid expansion with colloidal fluids can help reduce the risk for nephrotoxicity during treatment (**CIII**). The frequency of nephrotoxicity is lower for liposomal or lipid-associated preparations than for conventional amphotericin B. Conventional amphotericin B treatment might be associated with an increased risk of anemia.

Cases of newly symptomatic visceral and cutaneous leishmaniasis have been reported in association with the immune reconstitution syndrome following initiation of ART. However, existing experience regarding IRIS-associated leishmaniasis is insufficient to provide data for specific IRIS management guidelines. Leishmaniasis that manifests after initiation of ART requires specific therapy consistent with guidelines for initial treatment or management of relapse.

Management of Treatment Failure

For patients who fail to respond to initial therapy or experience a relapse after initial treatment, a repeat course of the initial regimen, or one or more of the recommended alternatives for initial therapy as outlined above, should be used (**AIII**). The response rate for retreatment appears to be similar to that for initial therapy, although certain patients might evolve to a chronic disease state with serial relapses despite aggressive acute and maintenance therapies.

Preventing Recurrence

Clinical cure is dependent on concurrent T-cell-mediated parasite killing. Relapses, particularly of visceral leishmaniasis and disseminated cutaneous leishmaniasis, commonly follow cessation of therapy among immunosuppressed patients with AIDS. Among patients with visceral leishmaniasis who are not receiving or

responding to ART, the risk of relapse at 6 and 12 months, in the absence of secondary prophylaxis (chronic maintenance therapy), is 60% and 90%, respectively. Therefore, secondary prophylaxis with an effective antileishmanial drug, administered at least every 2 to 4 weeks, is recommended, particularly for patients with visceral leishmaniasis and CD4+ counts <200 cells/microliter (**AII**). However, existing data are insufficient to recommend a specific regimen.

Daily allopurinol, in a dose of 300 mg three times daily, used for maintenance therapy is less effective than monthly pentavalent antimony and is not recommended (**DIII**). Although no published data on efficacy are available, maintenance therapy might be offered in immunocompromised patients with cutaneous leishmaniasis with multiple relapses after adequate treatment.

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

Although data are insufficient to provide a recommendation, discontinuation of secondary prophylaxis after successful treatment of leishmaniasis might be considered after a sustained (i.e., >3 to 6 months) increase in the CD4+ count to levels >350 cells/microliter after initiation of ART (**CIII**).

Special Considerations During Pregnancy

Diagnostic considerations are the same among pregnant women as in nonpregnant women. Labeling for pentavalent antimony compounds (sodium stibogluconate available in the U.S. through CDC and meglumine antimoniate) states that they are contraindicated for use among pregnant women, although various antimonial compounds were not teratogenic among chickens, rats, or sheep. Good clinical and pregnancy outcomes have been reported for three pregnant women treated with meglumine antimoniate and five women treated with liposomal amphotericin B. Because of concerns about toxicity and lack of experience with use of pentavalent antimony compounds in human pregnancy, amphotericin B is the first choice for therapy of visceral leishmaniasis in pregnancy (**AIII**). Pentavalent antimony should be the second choice (**AIII**). Miltefosine is teratogenic and is contraindicated in pregnancy. Perinatal transmission of *Leishmania* spp. occurs rarely; eight documented cases have been reported.

No data on the risk of transmission of *Leishmania spp*. among HIV-infected pregnant women are available.

Chagas Disease

Preventing Exposure

The reduviid insect vector of Chagas disease typically infests cracks and roofing of poor quality buildings constructed of adobe brick, mud, or thatch. The insects feed at night, and therefore HIV-infected persons living or visiting in areas where Chagas is endemic should avoid overnight stays in such dwellings or sleeping outdoors. They also should be aware that blood products in the U.S. or abroad might not always be screened routinely for *T. cruzi*. Transfusion, organ transplantation, and MTCT are the more likely infection routes in the U.S. Better

housing conditions and less efficient vectors might explain the lower risk of vectorial transmission in this country.

No drugs or vaccines for preventing *Trypanosoma (T.) cruzi* infection are available. Preventive measures include spraying infested dwellings with residual-action insecticide and if sleeping outdoors or in suspect dwellings cannot be avoided then sleeping under insecticide-treated bednets.

Preventing Disease

The clinical manifestations of Chagas disease in HIV-positive persons usually represent reactivation and not acute infection with *T. cruzi*. All HIV-infected persons with epidemiologic risk factors for Chagas disease should be tested for antibody to *T. cruzi* to detect latent infection. Antibody-positive patients who have not been previously treated, who are likely to have been infected for less than two decades, and who are without signs or symptoms of Chagas disease might benefit from a single course of medication with benznidazole or nifurtimox (**CIII**). Limited data and a lack of consensus exist regarding the benefit of chemotherapy in patients with longer-standing infection or chronic disease manifestations.

Optimization of ART might help prevent Chagas reactivation. The majority of cases have occurred in patients who were not taking ART.

Treatment of Disease

Chemotherapy of Chagas disease with benznidazole or nifurtimox is effective in reducing parasitemia and preventing clinical manifestations for patients with acute, early chronic, and reactivated disease. However, these drugs are limited in achieving parasitological cure. Consultation with a specialist should be sought. Benznidazole, 5 to 8 mg/kg body weight/day for 30 to 60 days, is the initial treatment most commonly recommended (**BIII**). Nifurtimox, 8 to 10 mg/kg body weight/day, administered for 90 to 120 days, is an alternative (**CIII**). However, the duration of therapy with either of these agents has not been studied for persons coinfected with HIV. Mortality is high, even in patients who receive chemotherapy. Limited data suggest that early recognition and treatment of reactivation might improve prognosis. Neither anti-trypanosomal drug is licensed in the U.S.; however, the drugs are available from the CDC Drug Service (404-639-3670) for use under investigational protocols.

ART is likely to reduce or prevent initial reactivation of *T. cruzi* or its recurrence. ART should be initiated or optimized once a patient with acute disease is clinically stable (**AIII**).

Monitoring and Adverse Effects, Including IRIS

Patients undergoing treatment should be closely monitored because both benznidazole and nifurtimox are toxic. Benznidazole causes peripheral neuropathy, rash, and granulocytopenia. Nifurtimox causes anorexia, nausea, vomiting, abdominal pain and weight loss, restlessness, tremors, and peripheral neuropathy. The adverse effects of both drugs wane when the drugs are discontinued.

No reports are available regarding *T. cruzi* infection and IRIS.

Management of Treatment Failure

Although no data are available, retreatment with benznidazole or nifurtimox is recommended for HIV-infected patients who fail to respond or who relapse following initial therapy (**AIII**).

Preventing Recurrence

Patients with HIV infection are potentially at risk for recurrent or relapsing clinical manifestations because of intermittent reactivation of chronic infection. The drugs are only partially effective in the chronic stage of disease, are suppressive rather than curative, and probably require lifelong administration to prevent relapse in the setting of continued immunosuppression. Because the drugs are toxic and experience with their use in HIV-infected patients is limited, expert advice about indicators and regimens should be sought. Whether secondary prophylaxis or chronic maintenance therapy should be used in HIV-infected patients with latent Chagas disease is unclear, particularly when modern ART is used.

Special Considerations During Pregnancy

The seroprevalence of *T. cruzi* infection among pregnant women in areas where the disease is endemic in Latin America ranges from as high as 50% in urban areas to 81% in rural areas. In the U.S., seroprevalence data are limited, but one study of 3,765 pregnant women in Houston, Texas, confirmed antibody to *T. cruzi* in 0.4% of Hispanic women and 0.1% of non-Hispanic women.

Perinatal transmission rates among general populations of pregnant women seropositive for antibodies to *T. cruzi* range from 2% to 10%. The effect of concurrent HIV infection in the mother on risk of perinatal transmission of *T. cruzi* is not known; however, limited data available at present suggest that rates of perinatal transmission might be higher for HIV-infected women than the rates previously documented for immunocompetent mothers. Infants coinfected with HIV and *T. cruzi* might be more likely to have symptoms, especially neurologic symptoms.

Congenital infection with *T. cruzi* might increase the risk for spontaneous abortion, stillbirth, and low birthweight. Congenital Chagas disease in newborn infants ranges from subclinical to life-threatening with severe neurological and cardiac disease.

Minimal data are available on potential reproductive toxicity of these drugs, although both drugs have been associated with increased detection of chromosomal aberrations in children being treated for Chagas disease. Benznidazole crosses the placenta in rats and covalently binds to fetal proteins. Because of the toxicity and limited experience with use of these drugs in pregnancy, treatment of acute *T. cruzi* infection among pregnant women should only be undertaken in consultation with a specialist in this area, and treatment of chronic disease should be considered after completion of the pregnancy. For HIV--

infected pregnant women with symptomatic reactivation of *T. cruzi* infection, the immune response should be maximized with ART (**AIII**).

Isosporiasis

Preventing Exposure

Not applicable to residents of the U.S.

Preventing Disease

In some settings, chemoprophylaxis with TMP-SMX has been associated with a lower incidence or prevalence of isosporiasis. In a randomized, placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against isosporiasis in persons with early-stage HIV infection (WHO clinical stage 2 or 3 at enrollment). In an observational study, the incidence of isosporiasis decreased after widespread introduction of ART, except among persons with CD4+ counts <50 cells/microliter. After adjustment for the CD4+ count, the risk of isosporiasis was substantially lower among persons receiving prophylaxis with TMP-SMX, sulfadiazine, or pyrimethamine (unspecified regimens). In analyses of data from a county AIDS surveillance registry during the pre-ART era, the prevalence of isosporiasis was lower in persons with (vs. without) a history of PCP—indirect evidence of a protective effect from use of TMP-SMX for PCP. However, insufficient evidence is available to support a general recommendation for primary prophylaxis for isosporiasis per se (**DIII**).

Treatment of Disease

Clinical management includes fluid and electrolyte support for dehydrated patients and nutritional supplementation for malnourished patients (**AIII**). TMP-SMX is the antimicrobial agent of choice for treatment of isosporiasis (**AI**). It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or treatment failure (**AIII**).

On the basis of initial studies, the traditional treatment regimen has been a 10-day course of TMP-SMX (160/800 mg) administered four times a day (**AII**). In a more recent study, TMP-SMX (160/800 mg) administered twice a day was effective (**BI**). Although experience using two versus four daily doses of TMP-SMX (160/800 mg) is limited, one approach would be to start with this regimen but to increase the daily dose and/or the duration of therapy (up to 3 to 4 weeks) if symptoms worsen or persist (**BIII**). Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption.

Limited data suggest that therapy with pyrimethamine–sulfadiazine and pyrimethamine–sulfadoxine might be effective. However, the combination of pyrimethamine plus sulfadoxine is not typically recommended for use in the U.S. (**CIII**); it has been associated with an increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome, and pyrimethamine and sulfadoxine are slowly cleared from the body after therapy is discontinued.

Single-agent therapy with pyrimethamine has been used with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50 to 75 mg/day) — plus leucovorin (10 to 25 mg/day) to prevent myelosuppression — might be an effective treatment alternative (e.g., it is the traditional option for sulfa-intolerant patients) (**BIII**).

Monitoring and Adverse Events, Including IRIS

Patients should be monitored for clinical response and adverse events. Among patients with AIDS, TMP-SMX therapy is commonly associated with side effects (e.g., rash, fever, leukopenia, thrombocytopenia, elevated transaminase levels). IRIS has not been reported in association with treatment of isosporiasis.

Management of Treatment Failure

If symptoms worsen or persist despite approximately 5 to 7 days of TMP-SMX therapy, the possibilities of noncompliance, malabsorption, and concurrent infections/enteropathies should be considered; the TMP-SMX regimen (i.e., daily dose, duration, and mode of administration) also should be reevaluated. For patients with documented sulfa intolerance or treatment failure, use of a potential alternative agent (e.g., pyrimethamine) should be considered. Ciprofloxacin might be considered as a second-line agent (**CI**). On the basis of limited data from a randomized, controlled trial in Haiti, ciprofloxacin (500 mg twice daily for 7 days) is less effective than TMP-SMX but might have modest activity against *Isospora (I.) belli*.

Unsubstantiated or mixed data are available for albendazole, nitazoxanide, doxycycline, the macrolides roxithromycin and spiramycin, and the veterinary anticoccidial agent diclazuril (**CIII**). Limited data suggest that drugs such as metronidazole, quinacrine, iodoquinol, paromomycin, and furazolidone are ineffective (**DIII**). Apparent or partial responses, if noted, might be attributable to treatment of concomitant infections or to nonspecific effects.

Preventing Recurrence

Patients with $CD4^+$ counts <200 cells/microliter should receive secondary prophylaxis (chronic maintenance therapy) with TMP-SMX (**AI**). In studies in Haiti, approximately 50% of patients who did not receive secondary prophylaxis had symptomatic recurrences approximately 2 months after completing a course of TMP-SMX therapy, relapses rapidly responded to retreatment, and secondary prophylaxis decreased the risk for relapse. In a randomized, placebo-controlled trial, no symptomatic recurrences were noted among patients who received maintenance therapy with thrice-weekly TMP-SMX (160/800 mg) (**AI**). Daily TMP-SMX (160/800 mg) and thrice-weekly TMP-SMX (320/1,600 mg) have been effective (**BIII**).

In sulfa-intolerant patients, pyrimethamine (25 mg/day) with leucovorin (5 to 10 mg/day) has been used (**BIII**). Ciprofloxacin (500 mg thrice weekly) might be considered as a second-line alternative (**CI**).

Discontinuing Secondary Prophylaxis

The concern of discontinuing prophylaxis has not been evaluated in a clinical trial. Chemoprophylaxis probably can be safely discontinued in patients without evidence of active *I. belli* infection who have a sustained increase in the CD4+ count to levels >200 cells/microliter for >6 months after initiation of ART (**BIII**).

Special Considerations During Pregnancy

TMP-SMX is usually the agent of choice for primary treatment and secondary prophylaxis in pregnant women, as it is for nonpregnant women. Although first-trimester exposure to trimethoprim might be associated with a small increased risk of birth defects, in the setting of maternal symptomatic *I. belli* infection, therapy with TMP-SMX should be provided. Because of concerns about possible teratogenicity associated with drug exposure during the first trimester, clinicians might withhold secondary prophylaxis during the first trimester and treat only symptomatic infection. Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk of defects. Human data about the use of ciprofloxacin during several hundred pregnancies have not suggested an increased risk of birth defects or cartilage abnormalities.

Definitions:

Strength of the Recommendation

A. Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. **Should always be offered**.
B. Moderate evidence for efficacy – or strong evidence for efficacy but only limited clinical benefit – supports recommendation for use. **Should generally be offered**.
C. Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the treatment or alternative approaches. **Optional**.
D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should generally not be offered**.
E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should never be offered**.

Quality of Evidence Supporting the Recommendation

I: Evidence from at least one properly designed randomized, controlled trial.

II: Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.

III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

CLINICAL ALGORITHM(S)

The original guideline document contains a clinical algorithm for the diagnosis of latent tuberculosis infection.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for many of the recommendations (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate prevention and treatment of opportunistic infections in human immunodeficiency virus (HIV)-infected adults and adolescents

POTENTIAL HARMS

Adverse Effects and Drug-Drug Interactions

- Major toxicities and interactions of the drug preparations used in treatment of opportunistic infections (OIs) are discussed in the "Major Recommendations" field of this summary under the "Monitoring and Adverse Events, Including IRIS" sections for each OI.
- Tables in the original guideline document provide information on common toxicities of agents for treatment and prevention of OIs (Table 5), substantial pharmacokinetic drug-drug interactions of for drugs used in the treatment of OIs (Table 6), and antiretroviral anti-infective drug combinations that should be avoided (Table 7).

Special Population – Pregnant Women

- Toxicities in pregnant women, fetuses, and neonates are discussed in the "Major Recommendations" field of this summary under the "Special Considerations During Pregnancy" sections for each OI.
- Table 9 in the original guideline document presents a summary of preclinical and human data on and indications for OI drugs during pregnancy.

See also the "Contraindications" field of this summary.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Live attenuated influenza vaccine should not be used during pregnancy.
- Doxycycline and other tetracyclines should not be used during pregnancy because of hepatotoxicity and staining of fetal bones and teeth.

- Because of their risk for teratogenicity, azoles should not be used during the first trimester of pregnancy.
- Pregnant women should not receive varicella vaccine.
- Podophyllin and podofilox should not be used during pregnancy. Use of podophyllin has been associated with an increased risk for fetal death in several animal models and case reports in humans, but not with congenital anomalies.
- For patients receiving intravenous cidofovir, blood urea nitrogen, creatinine, and urinalysis should be performed before each infusion; administration of the drug is contraindicated if renal dysfunction or proteinuria is detected.
- Contraindications for the use of ribavirin include unstable cardiopulmonary disease, pre-existing anemia unresponsive to erythropoietin, renal failure, or hemoglobinopathy.
- Both interferon (IFN) and ribavirin (RBV) are contraindicated in pregnancy.
- IFN is contraindicated in end-stage liver disease (ESLD) or decompensated liver disease.
- Labeling for pentavalent antimony compounds (sodium stibogluconate available in the United States through CDC and meglumine antimoniate) states that they are contraindicated among pregnant women, although various antimonial compounds were not teratogenic among chickens, rats, or sheep.
- Miltefosine is teratogenic and is contraindicated in pregnancy.
- Treatment for hepatitis C virus (HCV) infection with pegIFN plus RBV should NOT be routinely administered to persons in whom the potential risks of therapy are judged to outweigh the potential benefits including (but not limited to) persons with the conditions listed in the "Major Recommendations" field in the section "Treatment Recommendations" for HCV infection.
- BCG (bacillus Calmette-Guérin) vaccination for human immunodeficiency virus (HIV)-infected persons is contraindicated because of its potential to cause disseminated disease.
- Live attenuated influenza vaccine is contraindicated for HIV-infected persons.
- Because the interaction of RBV and didanosine might lead to clinically significant inhibition of mitochondrial DNA polymerase gamma, resulting in severe pancreatitis, lactic acidosis and, in some patients, death, the combination of RBV and didanosine is strictly contraindicated.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These guidelines are intended for clinicians, other health-care providers, human immunodeficiency virus (HIV)-infected patients, and policy makers residing in the United States; guidelines pertinent to other regions of the world, especially countries with limited resources, might differ regarding the spectrum of opportunistic infections (OIs) of interest and their diagnostic and therapeutic capacity.
- They are written for physicians and other health-care providers who care for human immunodeficiency virus (HIV)-infected persons in the United States and Western Europe where access is available to a full range of up-to-date medical services; however, these recommended strategies might not be feasible or appropriate in all settings where the spectrum of HIV-related

complications and diagnostic capacity differ from those observed in the United States and Western Europe.
- The guidelines are intended to complement more comprehensive textbooks, journals, and other relevant informational materials.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H, Centers for Disease Control and Prevention (CDC), National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009 Apr 10;58(RR-4):1-207; quiz CE1-4. PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Dec 17 (revised 2009 Apr 10)

GUIDELINE DEVELOPER(S)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

DHHS Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Henry Masur, MD (*Co-Chair*) National Institutes of Health, DHHS, Bethesda, MD; Jonathan E. Kaplan, MD (*Co-Chair*) Centers for Disease Control and Prevention, DHHS, Atlanta, GA; King K. Holmes, MD, PhD (*Co-Chair*) University of Washington, Seattle, WA; Constance Benson, MD (*Co-Chair*) University of California San Diego, CA; John T. Brooks, MD (*Editor*) Centers for Disease Control and Prevention, DHHS, Atlanta, GA; Alice Pau, PharmD (*Editor*) National Institutes of Health, DHHS, Bethesda, MD

Working Groups

Introduction, Leaders, Jonathan E. Kaplan, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Constance Benson, MD, University of California San Diego, CA, John T. Brooks, MD and Judith Currier, MD, University of California Los Angeles, CA

***Pneumocystis* Pneumonia, Leader**, Joseph Kovacs, MD, National Institutes of Health, DHHS, Bethesda, MD, Members, Hansjakob Furrer, MD, University Hospital and University of Bern, Switzerland, Laurence Huang, MD, San Francisco General Hospital, San Francisco, CA, Alison Morris, MD,MS, University of Pittsburgh Medical School, Pittsburgh, PA, Caryn G. Morse, MD, National Institutes of Health, DHHS, Bethesda, MD

***Toxoplasma gondii* Encephalitis, Leader**, Joseph Kovacs, MD, National Institutes of Health, DHHS, Bethesda, MD, Members, Letha Healey, MD, National Institutes of Health, DHHS, Bethesda, MD, Daniel Podzamczer, MD, Hospital Universitari de Bellvitge, Spain, José Miró, MD, PhD, Hospital Clinic- IDIBAPS. University of Barcelona, Spain

Cryptosporidiosis, Bacterial Enteric Infections, Leader, Timothy Flanigan, MD, Brown Medical School, Providence, RI, Members, John T. Brooks, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Cynthia L. Sears, MD, Johns Hopkins School of Medicine, Baltimore, MD, Christine Wanke, MD, Tufts University School of Medicine, Boston, MA, Clinton White, MD, University of Texas Medical Branch, Galveston, TX

Microsporidiosis, Leader, Louis Weiss, MD, MPH, Albert Einstein College of Medicine, Bronx, NY, Members, Elizabeth S. Didier, PhD, Tulane National Primate Research Center, Covington, LA, Caspar Franzen, MD, Universität Regensburg, Germany

***Mycobacterium tuberculosis* Infection and Disease, Leaders**, Alyssa Finlay, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, M. Elsa Villarino, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Members, Hansjakob Furrer, MD, University Hospital and University of Bern, Switzerland, José M. Miró, MD, PhD, Hospital Clinic- IDIBAPS. University of Barcelona, Spain, Payam Nahid, MD, MPH, University of California San Francisco at San Francisco General Hospital, CA, Kent Sepkowitz, MD, Memorial Sloan Kettering Cancer Center, New York, NY, Sophia Siddiqui, MD, National Institutes of Health, DHHS, Bethesda, MD

Disseminated *Mycobacterium avium* Complex Disease, Leader, Fred Gordin, MD, Veterans Affairs Medical Center, Washington, DC, Members, David Cohn, MD, Denver Public Health, Denver, CO, Judith Currier, MD, University of California Los Angeles, CA, Susan Dorman, MD, Johns Hopkins University School of Medicine, Baltimore, MD, Robert Horsburgh, MD, Boston University School of Public Health, Boston, MA

Bacterial Respiratory Disease, Leader, Laurence Huang, MD, San Francisco General Hospital, San Francisco, CA, Members, Robert F. Miller, MD, University College London, United Kingdom, Alison Morris, MD, MS, University of Pittsburgh Medical School, Pittsburgh, PA, Michael S. Niederman, MD, Winthrop-University Hospital, Mineola, NY

Bacterial Enteric Infections, Leader, John T. Brooks, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Members, Cynthia L. Sears, MD, Johns Hopkins School of Medicine, Baltimore, MD, Christine Wanke, MD, Tufts University School of Medicine, Boston, MA, Clinton White, MD, University of Texas Medical Branch, Galveston, TX

Bartonellosis, Leader, Jane Koehler, MD, University of California San Francisco, CA Members, Nesli Basgoz, MD, Massachusetts General Hospital, Harvard Medical School, Boston, MA, Lynn Guptill-Yoran, DVM, PhD, Purdue University School of Veterinary Medicine, West Lafayette, IN, James Oleske, MD, University of Medicine and Dentistry of New Jersey, Newark, NJ

Syphilis, Leader, Kimberly Workowski, MD, Emory University, Atlanta, GA, Members, Michael Augenbraun, MD, SUNY Downstate Medical Center, Brooklyn, NY, Edward Hook III, MD, University of Alabama, Birmingham, AL, Peter Leone, MD, University of North Carolina, Chapel Hill, NC, Anne Rompalo, MD, Johns Hopkins School of Medicine, Baltimore, MD, Bradley Stoner, MD, PhD, Washington University in St. Louis, St. Louis, MO, George Wendel, MD, University of Texas Southwestern Medical School, Dallas, TX

Mucocutaneous Candidiasis, Leader, Jack Sobel, MD, Wayne State University Medical Center, Detroit, MI, Members, Luis Ostrosky-Zeichner, MD, University of Texas Health Science Center, Houston, TX, Sanjay G. Revankar, MD, Wayne State

University School of Medicine, Detroit, MI, Jose A. Vazquez, MD, Henry Ford Health System, Detroit, MI

Cryptococcosis, Histoplasmosis, Coccidiomycosis, and Aspergillosis, Leader, Neil Ampel, MD, Southern Arizona Veterans Affairs Health Care System, Tucson, AZ, Members, Carol A. Kauffman, MD, University of Michigan, Veterans Affairs Ann Arbor Healthcare System, MI, Peter G. Pappas, MD, University of Alabama School of Medicine, Birmingham, AL

Cytomegalovirus Disease, Leader, Paul D. Griffiths, MD, DSc, Royal Free and University College Medical School, United Kingdom, Members, Henry H. Balfour, Jr., MD, University of Minnesota, Minneapolis, MN, Douglas Jabs, MD, The Mount Sinai School of Medicine, New York, NY, Michael Polis, MD, National Institutes of Health, DHHS, Bethesda, MD, Stephen Spector, MD, University of California, San Diego, San Diego, CA

Herpes Simplex Virus Disease, HHV-6 and HHV-7, Varicella-Zoster Virus Diseases, and Human Herpesvirus-8 Disease, Leaders, John W. Gnann, Jr., MD, University of Alabama, Birmingham, AL, Anna Wald, MD, University of Washington, Seattle, WA, Members, Corey Casper, MD, MPH, University of Washington, Seattle, WA, David W. Kimberlin, MD, University of Alabama, Birmingham, AL, Peter Leone, MD, University of North Carolina, Chapel Hill, NC

Human Papillomavirus, Leader, Joel Palefsky, MD, University of California, San Francisco, San Francisco, CA, Members, Susan Cu-Uvin, MD, Brown Center for AIDS Research, Providence, RI, Eileen F. Dunne MD, MPH, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Kenneth H. Fife, MD, PhD, Indiana University School of Medicine, Indianapolis, IN, Kathleen Squires, MD, Jefferson Medical College, Philadelphia, PA, Howard D. Strickler, MD, MPH, Albert Einstein College of Medicine, Bronx, NY

Hepatitis B Virus Infection, Leader, Kenneth Sherman, MD, PhD, University of Cincinnati, Cincinnati, OH, Members, Barbara McGovern, MD, Tufts University School of Medicine, Jamaica Plain, MA, Mindie Nguyen, MD, MAS, Stanford University, Palo Alto, CA, Marion Peters, MD, University of California, San Francisco, San Francisco, CA

Hepatitis C Virus Infection, Leader, Mark Sulkowski, MD, Johns Hopkins University, Baltimore, MD, Members, Raymond Chung, MD, Massachusetts General Hospital, Boston, MA, Mamta Jain, MD, University of Texas Southwestern Medical Center, Dallas, TX, Margaret James Koziel, MD, Beth Israel Deaconess Medical Center, Boston, MA, Andrew Talal, MD, MPH, Weill Medical College of Cornell University, New York, NY

Progressive Multifocal Leukoencephalopathy/JC Virus Infection, Leader, Richard W. Price, MD, University of California San Francisco, San Francisco, CA, Members, Paola Cinque, MD, PhD, San Raffaele Scientific Institute, Milan, Italy, Igor J. Koralnik, MD, Beth Israel Deaconess Medical Center, Boston, MA, Christina M. Marra, MD, University of Washington, Seattle, WA, José M. Miró, MD, PhD, Hospital Clinic- IDIBAPS, University of Barcelona, Spain

Geographic OIs of Specific Consideration, Leaders, Monica Parise, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Pacharee Kantipong, (penicilliosis), MD, Chiangrai Regional Hospital, Thailand, Members, Jorge Alvar, MD, World Health Organization, Geneva, Caryn Bern, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Suwat Chariyalertsak, MD, DrPH, Chiang Mai University, Thailand, Barbara Herwaldt, MD, MPH, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, James Maguire, MD, MPH, Brigham and Women's Hospital, Baltimore, MD, Anne Moore, MD, PhD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Larry Slutsker, MD, MPH , Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Khuanchai Suparatpinyo, MD, Chiang Mai University, Thailand, Jose Vazquez, MD, Henry Ford Health System, Detroit, MI, Murray Wittner, MD, PhD, Albert Einstein College of Medicine, Bronx, NY

Pregnancy, Leader, Heather Watts, MD, National Institutes of Health, DHHS, Rockville, MD, Members, Jean R. Anderson, MD, Johns Hopkins University, Baltimore, MD, Lynne Mofenson, MD, National Institutes of Health, DHHS, Rockville, MD.

Pharmacologic Issues/Tables, Leader, Alice Pau, PharmD, National Institutes of Health, DHHS, Bethesda, MD, Members, Ian R. McNicholl, PharmD, University of California, San Francisco, San Francisco, CA, Charles A. Peloquin, PharmD, National Jewish Medical and Research Center, Denver, CO, Paul J. Weidle, PharmD, MPH, Centers for Disease Control and Prevention, DHHS, Atlanta, GA

Immunizations, Leader, Gina Mootrey, DO, MPH, Centers for Disease Control and Prevention, DHHS, Atlanta, GA

Other Participants, Judith Aberg, MD, New York University, New York, NY, Miriam J. Alter, PhD, University of Texas Medical Branch, Galveston, TX, Roberto Badaro, MD, University of California, San Diego, La Jolla, CA, A. Cornelius Baker, Whitman-Walker Clinic, Washington, DC, John Bartlett, MD, Johns Hopkins University, Baltimore, MD, John Bennett, MD, National Institutes of Health, DHHS, Bethesda, MD, Pedro Cahn MD, PhD, Fundación Huesped, Argentina, Victoria Cargill, MD, National Institutes of Health, DHHS, Seattle, WA, Kenneth Castro, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Richard E. Chaisson, MD, Johns Hopkins University, Baltimore, MD, Myron Cohen, MD, University of North Carolina, Chapel Hill, NC, Robert Eisinger, PhD, National Institutes of Health, DHHS, Bethesda, MD, Wafaa El-Sadr, MD, MPH, Harlem Hospital, New York, NY, Judith Feinberg, MD, University of Cincinnati, Cincinnati, OH, Kenneth A. Freedberg, MD, MSc, Harvard Medical School, Boston, MA, Jose M. Gatell, MD, PhD, Unidad de Enfermedades Infecciosas, Spain, Peter A. Gross, MD, Hackensack University Medical Center, Hackensack, NJ, Diane Havlir, MD, University of California, San Francisco, San Francisco, CA, Thomas M. Hooton, MD, University of Miami Miller School of Medicine, Miami, FL, Edward Janoff, MD, University of Colorado, Denver, CO, Grace John-Stewart, MD, PhD, MPH, University of Washington, Seattle, WA, Rupert Kaul, MD, PhD, University of Toronto, Canada, Mari Kitahata, MD, PhD, University of Washington, Seattle, WA, Jens Lundgren, MD, University of Copenhagen, Denmark, Scott McClelland, MD, MPH, University of Washington, Seattle, WA, Richard D. Moore, MD, MHS, Johns Hopkins University, Baltimore, MD, James Neaton, PhD, University of Minnesota, Minneapolis, MN, Benjamin J. Park, MD, Centers for Disease Control and

Prevention, DHHS, Atlanta, GA, Thomas C. Quinn, MD, Johns Hopkins University, Baltimore, MD, David Rimland, MD, Veterans Administration Medical Center, Decatur, GA, Paul E. Sax, MD, Brigham and Women's Hospital, Boston, MA, Kathleen Squires, MD, Jefferson Medical College, Philadelphia, PA, Michael Tapper, MD, Lenox Hill Hospital, New York, NY, Chloe Thio, MD, Johns Hopkins University School of Medicine, Baltimore, MD, David Thomas, MD, Johns Hopkins University, Baltimore, MD, Cindy M. Weinbaum, MD, MPH, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Thomas C. Wright, Jr., MD, Columbia University Medical Center, New York, NY

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Centers for Disease Control and Prevention (CDC), their planners, and their content specialists wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters, with the exception of Constance Benson and King K. Holmes. Dr. Benson discloses being on the Advisory Board for Merck, GlaxoSmithKline, and Boehringer Ingelheim; being a grant recipient for Gilead; and being a Data Safety Monitoring Board (DSMB) member for Achillion and JJR Australia. Her spouse also is a consultant for Merck, Gilead, Achillion, Monogram, and Vertex. Dr. Holmes discloses being a DSMB member of Merck, receiving an honorarium at the 2005 Infectious Diseases Society of America Conference, and serving on the Mycology Research Laboratories scientific advisory board. Presentations will not include any discussion of the unlabeled use of a product or a product under investigational use.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK. Treating opportunistic infections among HIV-exposed and infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004 Dec 17;53(RR-15):1-118. [693 references]

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Centers for Disease Control and Prevention (CDC) Web site.

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

A Continuing Education activity is available from the Centers for Disease Control and Prevention (CDC) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on December 23, 2004. This summary was updated on January 21, 2005, following the release of a public health advisory from the U.S. Food and Drug Administration regarding the use of nevirapine. This summary was most recently updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisories on Sustiva (efavirenz) and COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on February 21, 2006 following the U.S. Food and Drug Administration (FDA) advisory on Tequin (gatifloxacin). This summary was updated by ECRI on March 3, 2006 following the FDA advisory on varicella zoster immune globulin (VZIG). This summary was updated by ECRI on January 29, 2007, following the U.S. Food and Drug Administration advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on July 9, 2007, following the FDA advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on October 3, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Rocephin (ceftriaxone sodium). This summary was updated by ECRI Institute on November 9, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs. This summary was updated by ECRI Institute on February 26, 2008 following the U.S. Food and Drug Administration advisory/voluntary market withdrawal of the liquid formulation of Leukine (sargramostim). This summary was updated by ECRI Institute on March 21, 2008 following the FDA advisory on Erythropoiesis Stimulating Agents. This summary was updated by ECRI Institute on July 28, 2008 following the U.S. Food and Drug Administration advisory on fluoroquinolone antimicrobial drugs. This summary was updated by ECRI Institute on August 15, 2008 following the U.S. Food and Drug Administration advisory on Erythropoiesis Stimulating Agents (ESAs). This summary was updated by ECRI Institute on May 29, 2009.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public

or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 7/27/2009